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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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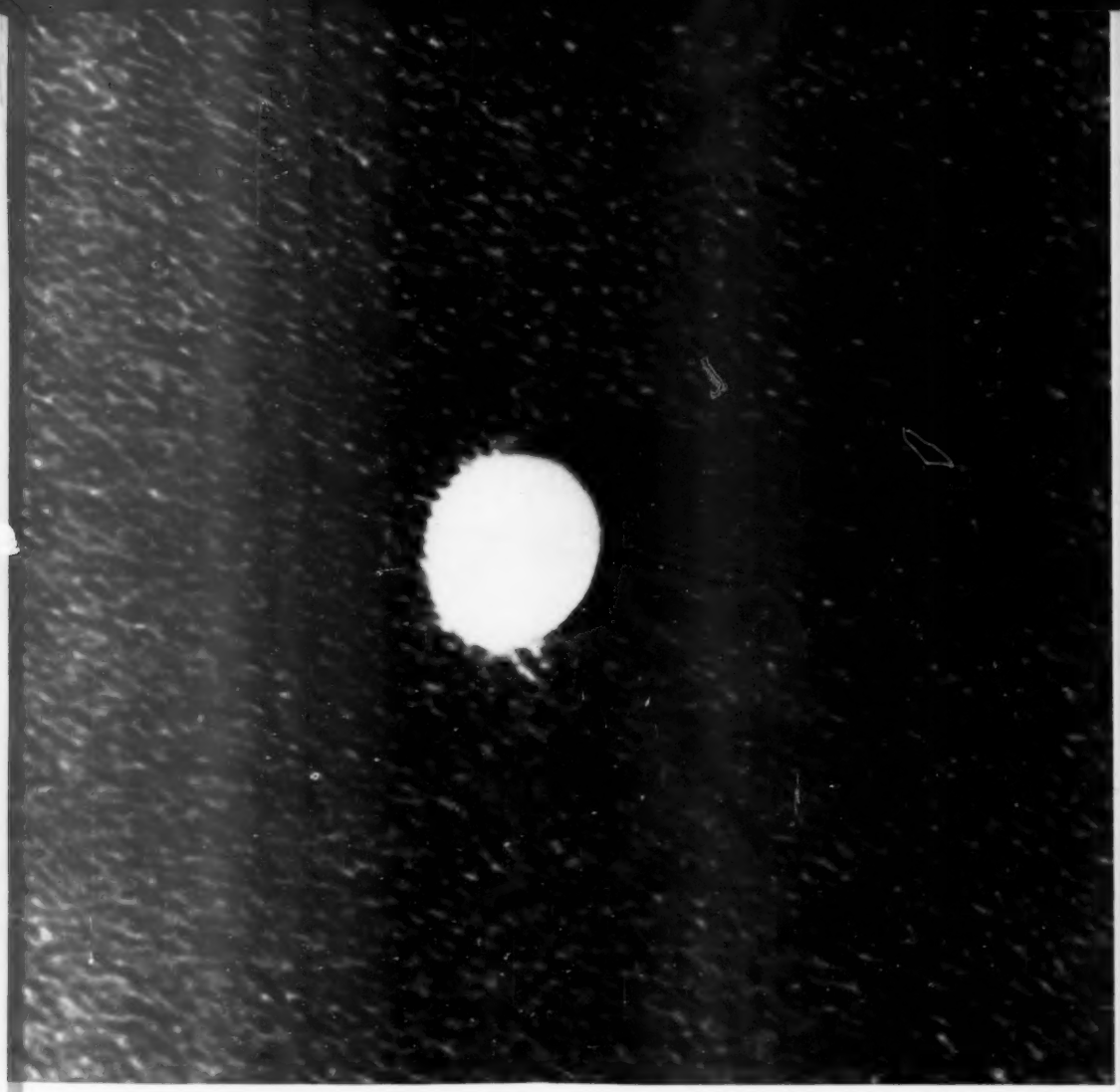

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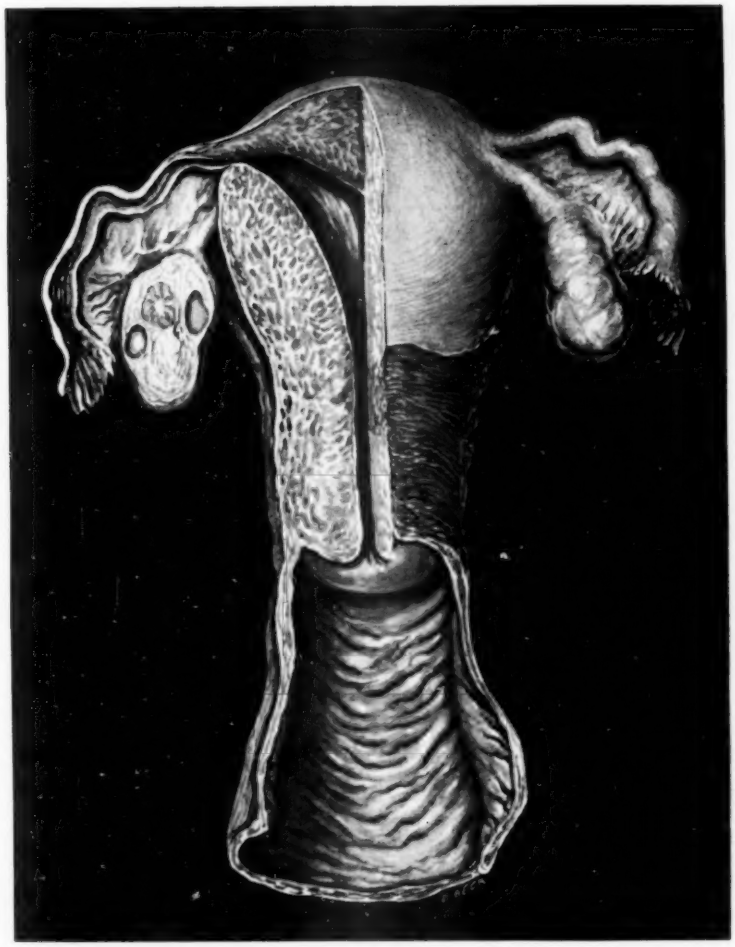

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*Sturnick, M. I., and Gargill, S. L.: New England J. Med. *247*:829 (Nov. 27) 1952.

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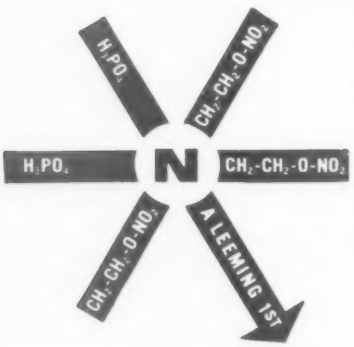
Angina pectoris prevention



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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ORIGINAL ARTICLES

THE TREATMENT OF COEXISTING ADDISON'S DISEASE AND ACTIVE PULMONARY TUBERCULOSIS*

By J. S. L. Browne, M.D.
PROFESSOR OF MEDICINE

M. Aronovitch, M.D.
LECTURER IN MEDICINE

J. C. Beck, M.D.
LECTURER IN MEDICINE

W. Leith, M.D.
DEMONSTRATOR IN MEDICINE

AND

J. F. Meakins, M.D.
LECTURER IN MEDICINE

(From The Royal Victoria Hospital and the McGill University Clinic, Montreal, Canada)

At the beginning of the ACTH and cortisone era, first Smith and then others demonstrated the initial improvement of symptoms in pulmonary tuberculosis by the administration of ACTH[4-11]. There was an amelioration of fever, diminished cough, increase in appetite and a return of a sense of well-being. The sputum cultures, however, remained positive for tuberculosis and in some cases there was a spread of the pulmonary lesions as demonstrated by Roentgen ray. On withdrawal of ACTH an abrupt flare-up of the illness occurred with further spread of the disease. Following these observations a number of reports appeared describing the reactivation of tuberculous foci during the administration of high doses of ACTH and cortisone for diseases other than tuberculosis[1,3,5,9,15,16].

Controlled studies on the experimental animal paralleled these clinical findings[2,10,13]. It was observed that ACTH and cortisone caused an acceleration of experimental tuberculosis in such animals as the mouse, guinea pig and rabbit. The mode of action is only

*Presented, in part, at the meeting of the Association of American Physicians at Atlantic City, New Jersey, May 4-5, 1954.

TABLE 1.—ADDISON'S DISEASE AND PULMONARY TUBERCULOSIS

					Treatment			Status—1954	
Case	Age	Sex	Addison's Disease Symptom Onset	Date of Discovery of Tbc	Addison's Cortisone mg. / NaCl gm. / Day		Anti-Tbc*	Clinical	Roentgen-ray
A. A.	50	F	May 1947	March 1950	1947–50	DCA A.C.E.	Apr.–Nov. 1950 Strep., PAS	Working since Jan. 1951 Cortisone 37.5 NaCl 6	No Activity
					Mar. 1950	Cortisone 50 NaCl 6			
D. P.	52	M	April 1950	1925–1930 Reactivation August 1950	Nov. 1950	Cortisone 50 NaCl 6	Nov. 1950 to Mar. 1951, Strep., PAS	Working since August 1952 Cortisone 12.5 NaCl 6	No Activity
Y. L.	59	M	May 1948	June 1950 Epididymitis 1951	May 1950 to Oct. 1951	DCA A.C.E.	Oct. 1951 to Sept. 1952, Strep., PAS	Working since Apr. 1953 Cortisone 25 NaCl 6	No Activity
					Oct. 1951	Cortisone 50 NaCl 6			
L. C.	32	M	May 1948	1942 Epididymitis 1943 Pott's Dis.	Mar. 1950	Cortisone 50 NaCl 6	Apr.–July 1952 Isonicotinic Acid 200 mg. Sept. 1952 PAS / Strep.	Not working Cortisone 37.5 NaCl 6	No Apparent Activity
E. C.	54	M	Nov. 1950	Nov. 1951	Nov. 1951	Cortisone 50 NaCl 6	Dec. 1951 to Mar. 1953, Strep., PAS	Return to work as orderly in T.B. san. July 1953 Cortisone 25 NaCl 6	No Activity

* Average dose: Strep. gm. 1 T.I.W.—PAS 12 gm./day.

partly understood. Lurie has conducted a detailed series of studies on this problem and his views probably reflect the prevailing opinion[7,8]. It is known that ACTH and cortisone suppress nonspecific and allergic inflammation by decreasing antibody formation, capillary permeability and round-cell migration. Phagocytosis of the invading organism is increased but the actual digestive capacity of the phagocytic cell is decreased. Inoculated experimental animals under the influence of these agents tend to isolate the infection from the rest of the body, but permit local multiplication of the bacteria. Organisms can thus accumulate in the tissues in the absence of fever and toxemia which have been suppressed by these hormones.

Streptomycin and para-aminosalicylic acid (PAS) became available for clinical use in tuberculosis only a short time before ACTH and cortisone[6,11]. The prognosis of cases of concomitant Addison's disease and active pulmonary tuberculosis before the advent of cortisone was poor[12]. Although the antituberculosis agents partially controlled the activity of the tuberculous process, the danger of further spread by the use of cortisone was still unknown. The use of cortisone in active tuberculosis remained a matter of individual assessment.

Clinical Material. During the interval between March, 1950, and November, 1951, we had the opportunity of observing 5 patients with concomitant Addison's disease and active pulmonary tuberculosis. There were 4 males whose ages when first seen with these two diseases ranged from 28 to 56 years, and one woman aged 46 years. The pertinent data concerning the individual patients is found in Table 1 and in the case reports.

The date of onset of the Addison's disease is of necessity an approximate one, estimated on the basis of the patient's history. The diagnosis of active pulmonary tuberculosis was only made when the chest roentgenogram suggested an active lesion which could be confirmed by the finding of tubercle bacilli on either smear or culture of the sputum or gastric washings.

In 2 patients (D.P., L.C.) there was a history of previous admissions to sanatoria for pulmonary tuberculosis, and in one of them for a tuberculous epididymitis and Pott's disease. They were both considered arrested in the interval until reactivation of the pulmonary disease was demonstrated.

All patients received 50 mg. of cortisone acetate and 6 gm. of supplemental sodium chloride daily as replacement therapy for the Addison's disease. Subsequent to arrest of the pulmonary tuberculosis the maintenance dose of cortisone has ranged from 12.5 to 37.5 mg. daily.

Upon substantiating the diagnosis of active pulmonary tuberculosis, streptomycin in an average dose of 1 gm. three times weekly and para-aminosalicylic acid (PAS) in an average dose of 12 gm. daily was instituted in 4 patients. This regimen was initiated at The Royal Victoria Hospital and was continued in a tuberculosis sanatorium until the disease was considered arrested.

In one patient (L.C.), who refused to come to hospital for streptomycin and PAS, administration of isonicotinic acid (Rimifon) 200 mg. daily was carried on for 4 months following which streptomycin and PAS was given on an outpatient basis. This patient remains the only one receiving antituberculous therapy.

All patients are followed regularly in the Endocrine Clinic of The Royal Victoria Hospital, and periodic Roentgen-ray examination of the chest is carried out.

Case Reports. CASE 1. (A.A.). A 43-year-old married woman was in good health until 1945, when she noticed the onset of weakness, fatigue and absence of perspiration. In 1946, she sought psychiatric aid because of anorexia and palpitations and a hypertension was discovered at this time. The first admission occurred in April, 1947, because of nausea, vomiting, extreme weakness and emotional instability of one week's duration. In addition generalized pigmentation had been apparent for 6 months, amenorrhea for 4 months and the hypertension had disappeared 3 months previous to her admission. Physical examination revealed a thin emaciated, dehydrated, markedly pigmented female weighing 90 pounds. The blood pressure was 80/60. Laboratory findings showed a blood sugar of 72 mg. per 100 cc. and nonprotein nitrogen of 59.5 mg. per 100 cc., serum sodium 132.5 mEq./L. Serum potassium was 5.5 mEq./L. The Addisonian crisis responded to large amounts of adrenal cortical extract and glucose saline. Further investigation revealed biological corti-

Fig. 1A

Fig. 1B

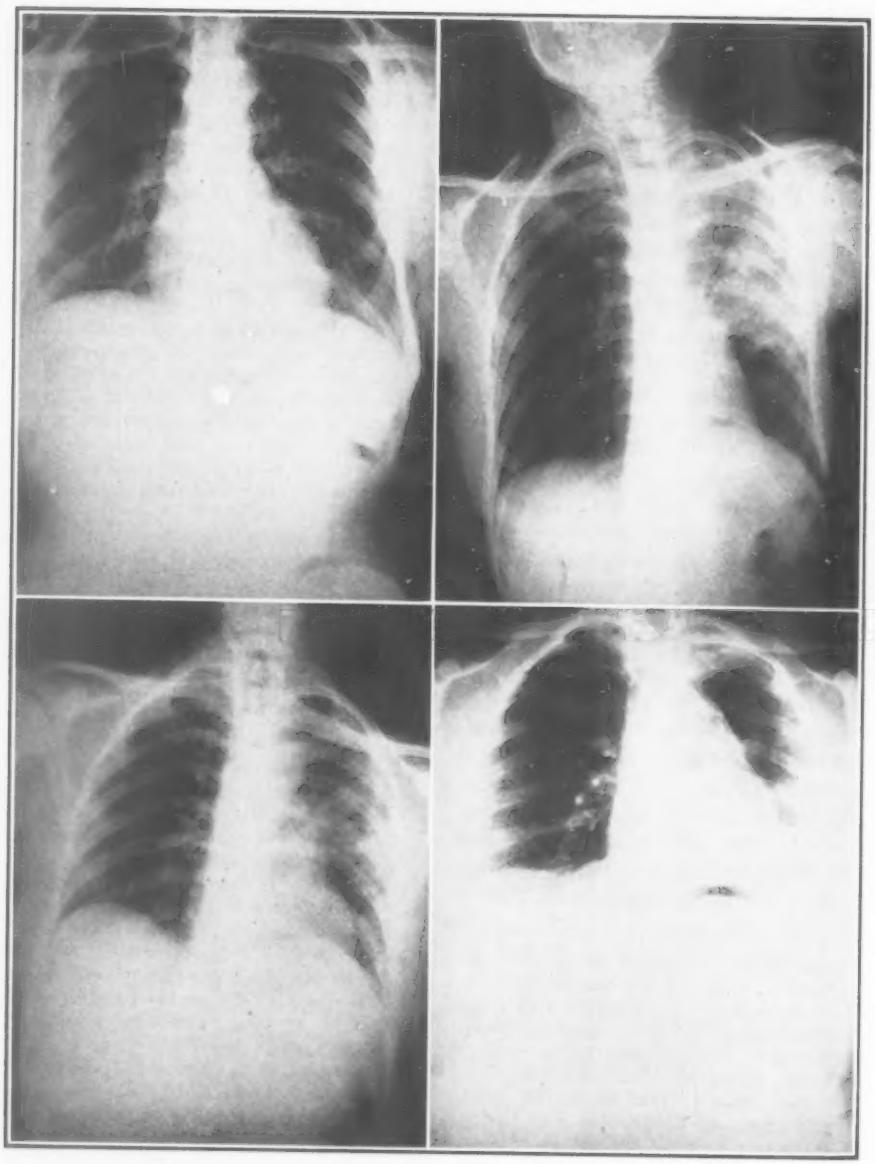

Fig. 1C

Fig. 1D

Fig. 1A.—(A.A.) Showing normal chest roentgenogram in 1948. 1B. (A.A.) March, 1950, demonstrates parenchymal lesion involving the left upper lobe before treatment. 1C. (A.A.) May, 1950, demonstrates clearing of the infiltration with early displacement of the heart and mediastium to the left. 1D. (A.A.) Demonstrates appearance of the chest roentgenogram on cessation of streptomycin administration in November, 1950.

coids below 15 Gl. units per 24 hours on repeated occasions and the 17 ketosteroids ranged from 1.4 to 4.7 mg./24 hours. The patient was maintained on DCA pellets, added sodium chloride and methyl testosterone 30 mg. daily, and was discharged 10 months after admission. Numerous readmissions occurred subsequently because of pain and spasm in the muscles of the lower extremities which progressed to marked contractures and was felt to be related to the DCA administration. On other occasions she was admitted in hypoglycemic coma and her emotional state was such that she would not cooperate with any physiotherapeutic procedures.

2 weeks later streptomycin 1 gm. daily and PAS 6 to 8 gm. daily were added. On this regimen there was marked improvement in the Addison's disease and definite clearing of the parenchymal infiltration was demonstrated on May 20, 1950 (Fig. 1C). There was some improvement in her ability to move the lower limbs and fading of the deep skin and mucous membrane pigmentation occurred. Three months after beginning cortisone therapy her hypertension and menses returned.

Treatment was continued at sanatorium until November, 1950, when the streptomycin was stopped and the pulmonary disease was considered arrested (Fig. 1D). There had

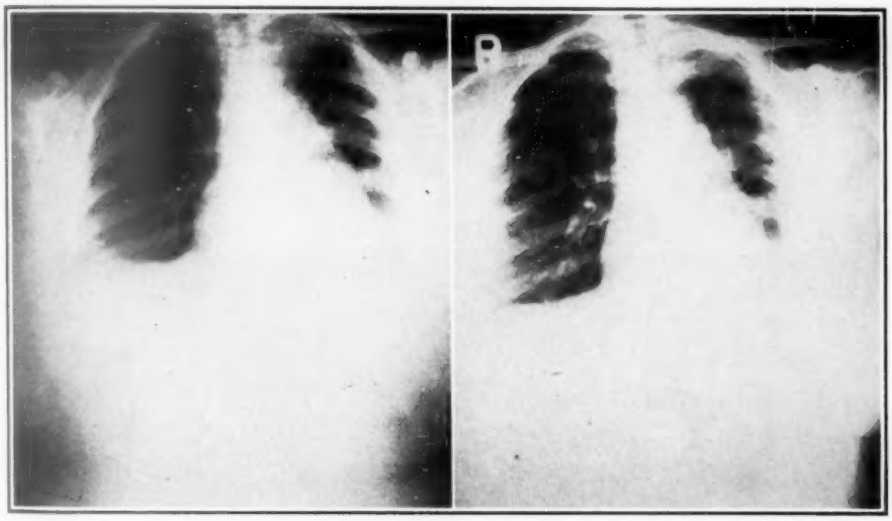

Fig. 2A Fig. 2B

Fig. 2A—(A.A.) Follow-up film in August, 1951. 2B. (A.A.) Follow-up film in 1952.

In March, 1950, this patient was admitted for a trial of cortisone in an attempt to improve the replacement therapy for the Addison's disease and also to correct the muscle contractures. Her weight had fallen to 72 pounds, the pigmentation was marked and flexion contractures of the hips and knees were present. In addition there was dullness to percussion and blowing breathing over the left upper chest. Roentgenogram of the chest showed an area of infiltration involving most of the upper lobe and gastric washings were reported positive on culture for tubercle bacilli 2 weeks later (Fig. 1B). Cortisone acetate, 50 mg. daily, was begun on March 14, 1950, and when the lesions were proven tubercular been definite improvement with a weight gain to 113 pounds, a blood pressure of 146/104, only very slight pigmentation was evident and the range of motion of the hips and knees had increased. The serum electrolytes and blood sugars were normal and the cortisone was reduced to 37.5 mg. per day with 6 gm. of supplementary sodium chloride. PAS was continued in a dose ranging from 8 to 15 gm. daily. The weight rose to 141 pounds, the blood pressure increased to 164/115 and she resumed work in January, 1951. Follow-up finds her in good health with no activity of the pulmonary lesion (Fig. 2).

CASE 2. (D.P.). A 48-year-old displaced person from Poland was admitted in October,

Fig. 3A Fig. 3B

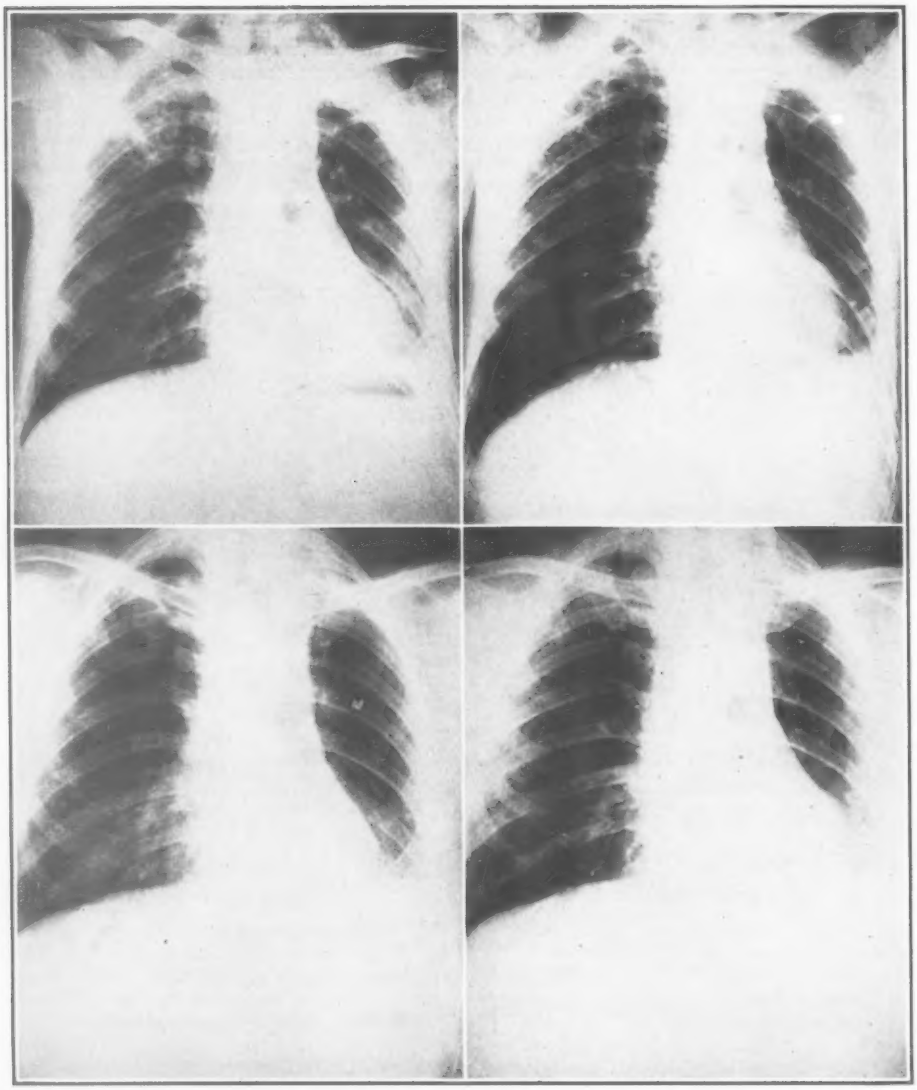

Fig. 3C Fig. 3D

Fig. 3A.—(D.P.) Demonstrates bilateral apical tuberculosis as seen in November, 1950, before beginning therapy. 3B. (D.P.) Demonstrates clearing of the infiltration in the right apex seen in January, 1951. 3C. (D.P.) Demonstrates further clearing at the right apex at the time when streptomycin was discontinued in March, 1951. 3D. (D.P.) Follow-up film in 1953.

1950, from a tuberculosis sanatorium because of persistent nausea, vomiting and hypotension (blood pressure 70/50) of 2 weeks' duration. There had been cough and expectoration for one month and pigmentation of the face, neck and elbows for 3 to 4 months. Past history revealed a 4 to 6 year hospitalization in Poland for pulmonary tuberculosis, final discharge from sanatorium having occurred in 1930. He had developed epigastric distress and constipation while in Italy, which had disappeared following his Army discharge. Six months prior to his admission to this hospital he had noticed anorexia, nausea and a 35 to 40 pound weight loss. During investigation at another hospital a hemoptysis occurred, and chest roentgenograms and sputum examination at this time showed the presence of active pulmonary tuberculosis, for which he was sent to sanatorium.

Physical examination on admission showed marked emaciation with a weight of 103 pounds, pulse rate 104/min., blood pressure 84/50. There was moderate dehydration of the skin and mucous membranes and there was deep pigmentation over the face, neck and upper thorax, the elbows and knees and in the palmar creases. There was no mucous membrane pigmentation. There was dullness to percussion and diminished breath sounds in the left apical region and in the right axilla, and rhonchi in the left subclavicular area. Laboratory examinations were as follows: Urine was negative, hemoglobin, 51%, white blood cell count 3,000 per c.mm., sedimentation rate, 66 mm. per hour; nonprotein nitrogen, 27.5 mg., per 100 cc.; serum sodium, 128 mEq./L., serum potassium, 4.24 mEq./L., serum chlorides 96 mEq./L., and CO_2-combining power 58.8 volumes %. The 17 ketosteroids were 2.0 mg. per 24 hours and the biological corticoids less than 15 glycogenic units per 24 hours. The ACTH test procedure showed a response characteristic of Addison's disease. Roentgenogram of the chest showed bilateral apical tuberculosis on November 22 (Fig. 3A). On cortisone, sodium chloride, streptomycin and PAS there was rapid clearing particularly in the right chest seen on examination on January 5, 1951 (Fig. 3B). There was marked clinical improvement with fading of the skin pigmentation and a rise in blood pressure from 100/70 to 110/75.

He was returned to sanatorium in January, 1951, and the streptomycin was discontinued on March 4, because of urticaria and blurring of vision. There was steady improvement, disappearance of the cough and sputum and a progressive weight gain. The blood pressure ranged from 110/70 to 120/72. Roentgen-ray examination of the chest on April 17 showed further clearing of the opacities in the right lung and 3 consecutive sputa were negative on smear and culture (Fig. 3C).

On re-evaluation in April, 1951, there were no complaints; the hemoglobin was 109%, the white blood count 10,000 per c.mm. The sedimentation rate was 5 mm. per hour and the fasting blood sugar 121 mg. per 100 cc. The serum electrolytes were as follows: sodium 124 mEq./L., potassium 6.26 mEq./L., and chloride 88.7 mEq./L. and inquiry revealed that he had neglected to take his supplementary sodium chloride. These returned promptly on 2 gm. of sodium chloride 3 times daily. The sputum and gastric washings were negative on culture and the weight had risen to 139 pounds.

Since that time he has remained well and has operated a small busines which he began on discharge.

CASE 3. (Y.L.). A 56-year-old Chinese laundry worker had complaints of weakness, a 28-pound weight loss and pigmentation for 2 years prior to admission in 1950. At that time he exhibited fever, anorexia, skin and mucous membrane pigmentation, a right testicular mass and absent breath sounds over the right lower lobe and sputum cultures were positive for tuberculosis. The serum sodium was 137.5 mEq./L., the blood sugar was normal, the 17 ketosteroids were 1.8 mg./24 hours and the corticoids 28 Gl. units/24 hours. The testicular mass was diagnosed as tuberculous epididymitis. He was discharged to a tuberculosis sanatorium on DCA 5 mg. 3 times per week and 6 gm. of NaCl/day. He remained there for one year on the above therapy in addition to PAS. The sputum cultures became negative. He was readmitted to the hospital in 1951, when the chest showed the presence of râles over the right apex, and the chest film activity at the right upper lobe (Fig. 4A). The sputum culture continued to be negative. The skin and mucous membrane pigmentation was still present. The blood pressure was 90/62 and the weight 100 pounds. The blood sugar was normal while the serum sodium was 131 mEq./L., the chloride 96.4 mEq./L., the potassium 4.54 mEq./L., the 17 ketosteroids 3.8 mg./24 hours and the corticoids 28 Gl. units/24 hours. Therapy was then instituted with 50 mg. of oral cortisone daily, streptomycin 1 gm. twice weekly and PAS 12 gm./day. The DCA was discontinued but the 6 gm. of sodium chloride/day continued. Within 3 weeks there was a decrease of the pigmentation and the electrolytes were back to normal levels with a sodium of 147 mEq./L., a chloride of 109

Fig. 4A Fig. 4B

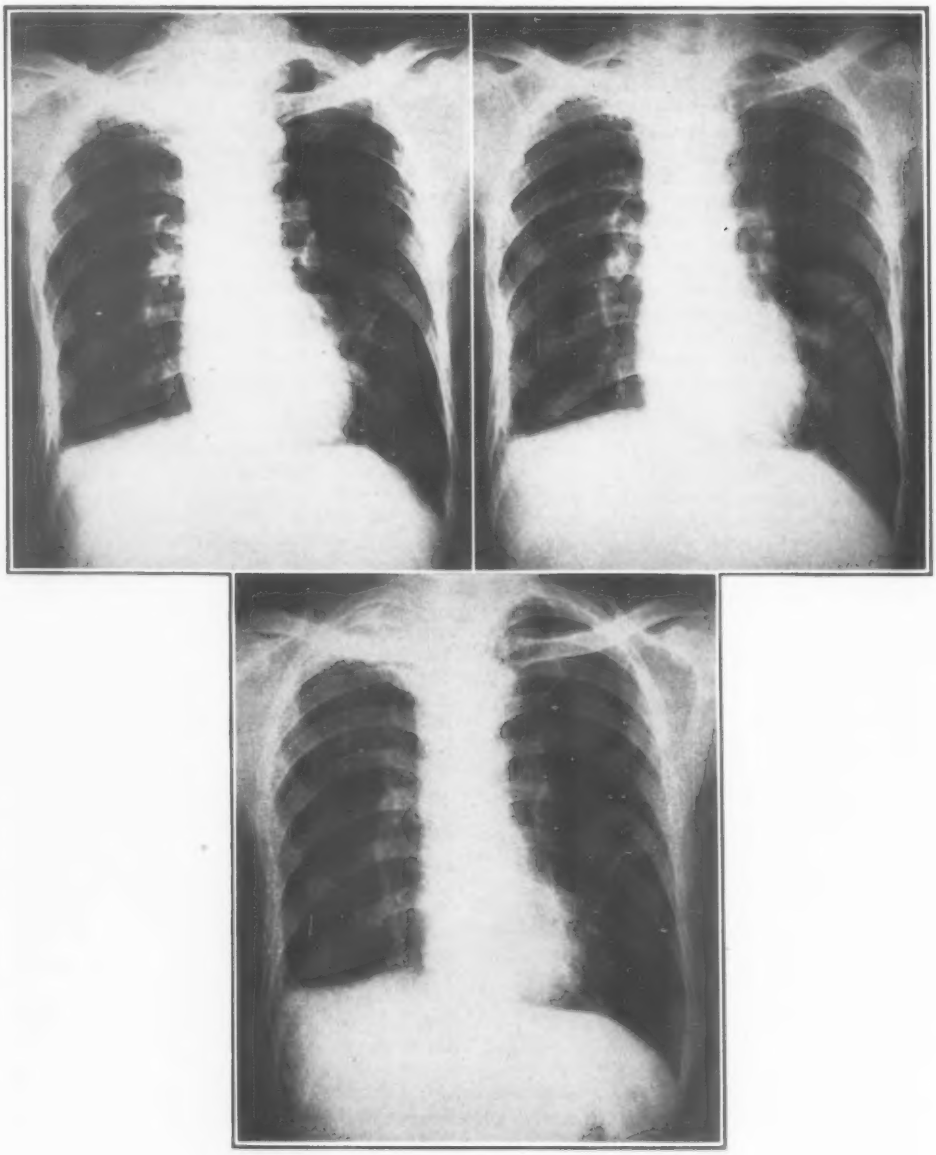

Fig. 4C

Fig. 4A.—(Y.L.) Showing an area of infiltration involving the right upper lobe observed before beginning cortisone and specific antituberculous therapy. 4B. (Y.L.) Three weeks after initiation of treatment showing clearing of the lesion at the right apex. 4C. (Y.L.) Follow-up examination in 1954.

mEq./L., and a potassium of 4.42 mEq./L. The blood pressure was 105/60. There was clearing of the infiltration in the right apex (Fig. 4B). There was no change in the urinary output of 17 ketosteroids or corticoids. He was then returned to the sanatorium on the above therapy and remained well until his discharge in 1952. At this time the streptomycin and PAS were stopped and his tuberculosis was considered arrested. The weight at this time was 134 pounds. The electrolytes remained at normal levels. He was put on 37.5 mg. cortisone per day and continued on this dose until 1953, when he returned to light work and the cortisone dosage was dropped to 25 mg./day. He has been well, maintaining the same weight with normal serum electrolyte and blood pressure levels (Fig. 4C).

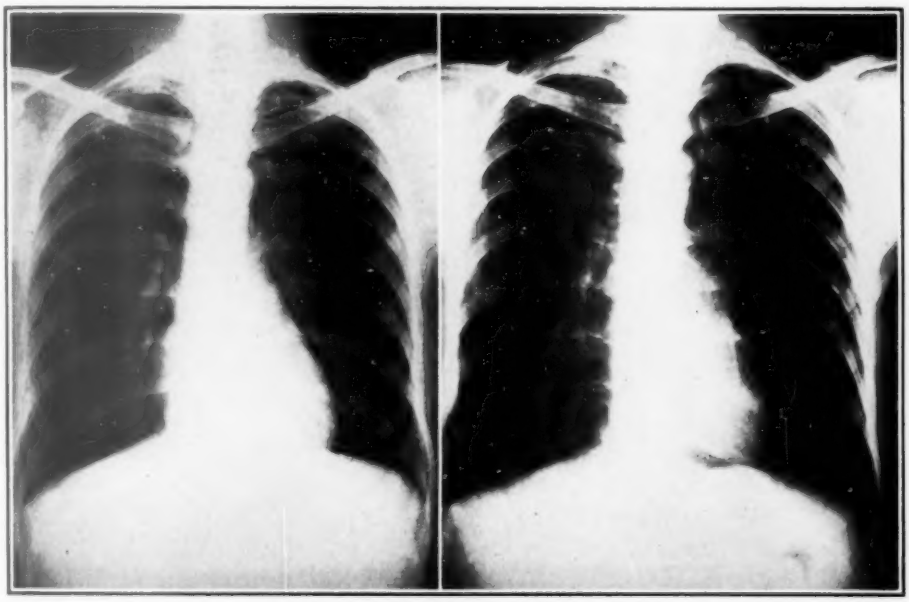

Fig. 5A Fig. 5B

Fig. 5A.—(L.C.) Demonstrates multiple calcific densities in both upper lobes as seen in September, 1950; an appearance which had been unchanged since 1944. 5B. (L.C.) The chest film has remained unchanged throughout this patient's treatment.

CASE 4. (L.C.). A 32-year-old man was first seen in this hospital in July, 1942. At that time a diagnosis of tuberculous epididymitis was made and confirmed when a right orchidectomy was carried out with satisfactory results. A hemoptysis had occurred one month before admission and roentgenogram of the chest showed bilateral pulmonary tuberculosis, confirmed by positive sputum on smear and culture. The patient was discharged to sanatorium and returned in November, 1943, with tuberculous Pott's disease and a plaster jacket was applied following which he was returned to sanatorium where he discharged himself as apparently arrested.

He remained well until 1948, when he noted nausea, occasional vomiting, marked fatigue and weakness, pigmentation, frequency and nocturia and a craving for salt. These symptoms were progressive and led to his readmission in March, 1950.

Physical examination revealed an emaciated male with deep skin and mucous membrane pigmentation. The blood pressure was 75/60, the hemoglobin 63%, the white blood cell count 7,800 per c.mm. and the sedimentation rate 18 mm./hour. The serum electrolytes were as follows: Sodium 125 mEq./L., potassium 5.75 mEq./L. and chlorides 88.4 mEq./L. There was a flat glucose tolerance curve. The epinephrine test led to no sig-

Fig. 6A Fig. 6B

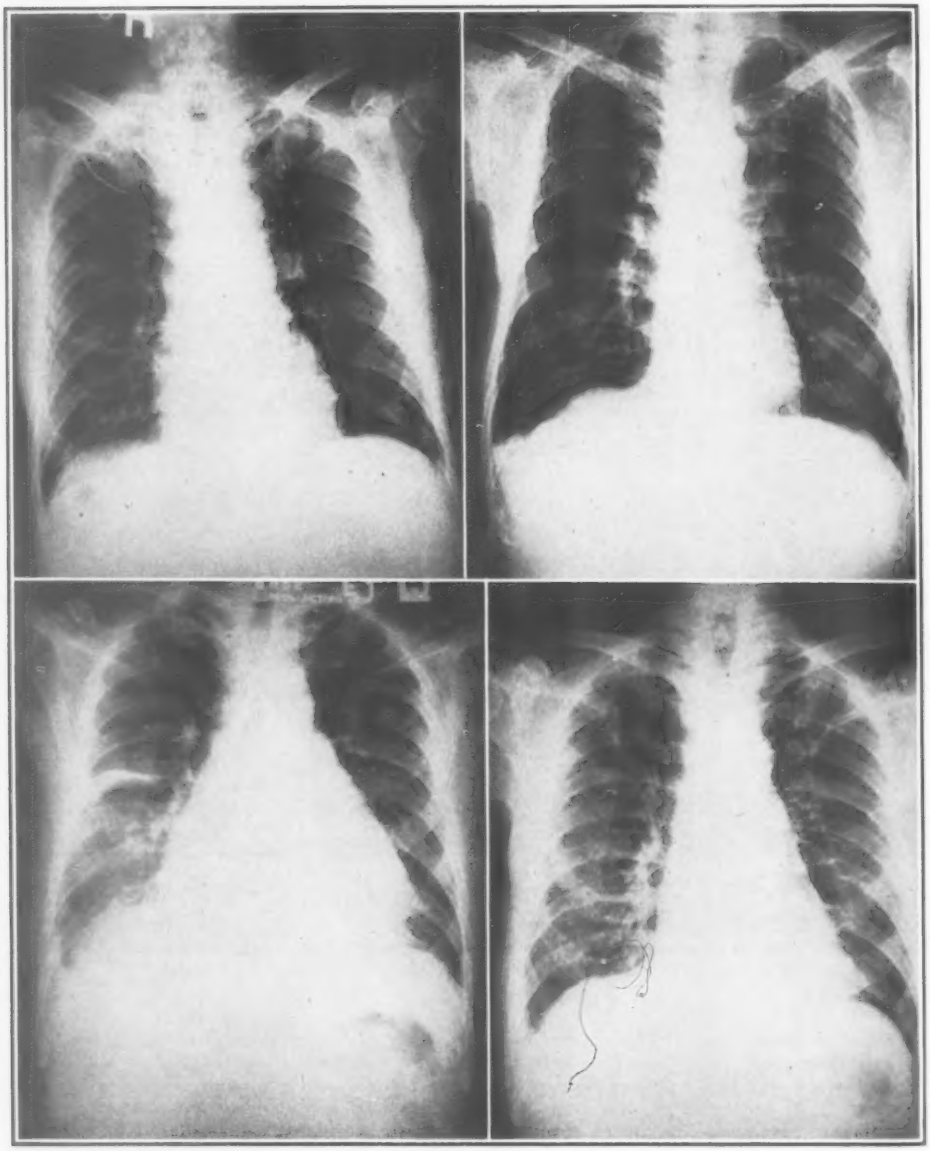

Fig. 6C Fig. 6D

Fig. 6A.—(E.C.) Appearance of the chest film just prior to cholecystectomy in November, 1951. There is an area of infiltration at the right apex which suggested an active lesion. 6B. (E.C.) Twenty-five days after beginning treatment showing definite clearing at the right apex. 6C. (E.C.) February 8, 1952, at which time a right pleural and pericardial effusion was demonstrated. 6D. (E.C.) February 12, 1952, demonstrates clearing of the pleural and pericardial effusion.

nificant fall in eosinophils and the 17-ketosteroids ranged between 1.3 and 2.5 mg./24 hours, roentgenogram of the chest showed multiple calcific densities in both upper lobes and three sputa were negative on smear and culture (Fig. 5A). Replacement therapy was begun with desoxycorticosterone and added sodium chloride but a hypoglycemic crisis occurred and maintenance cortisone acetate 50 mg. daily was begun with dramatic improvement.

Readmission occurred in September, 1950,

Fig. 7A

Fig. 7B

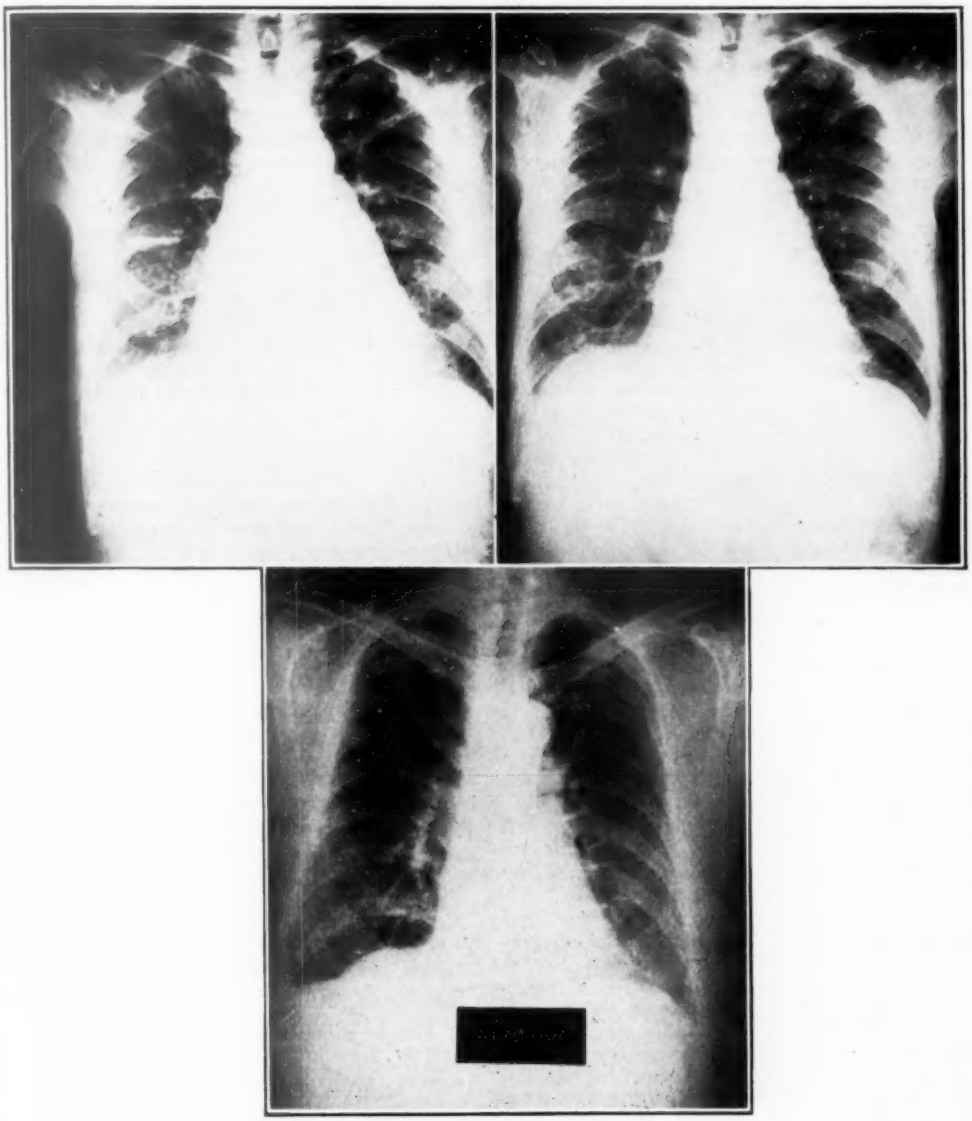

Fig. 7C

Fig. 7A.—(E.C.) Roentgenographic appearance when the pleural and pericardial effusion recurred several weeks later. 7B. (E.C.) Partial disappearance of these findings within 2 days. 7C. (E.C.) Follow-up examination in 1953.

because of increasing fatigue and weakness of 1-month duration. The blood pressure was 95/65 and the hemoglobin 90%. The serum sodium was 137.5 mEq./L., the serum potassium 4.16 mEq./L. and the serum chloride 100 mEq./L. The 17 ketosteroids ranged from 2.7 to 4.5 mg./24 hours. Four 125-mg. desoxycorticosterone acetate pellets were implanted and the cortisone was reduced to 37.5 mg. daily. Three sputa were reported positive on culture for tubercle bacilli after discharge, but the patient refused to come to hospital or sanatorium for treatment. There was no change in the chest roentgenogram at this time. Subsequently repeated sputum examinations were negative and it was not until December, 1951, that it was discovered that he was bringing a friend's sputum for examination. Gastric washings at this time and a laryngeal swab in January, 1952, were positive.

From April until July, 1952, the patient received isonicotinic acid hydrazide and in September, 1952, streptomycin and PAS administration was begun by a visiting nursing service. The first negative gastric washing occurred in 1953, and since that time there have been 6 negative examinations. There was no change in the chest film from the examination in 1950, which showed multiple calcific densities in both upper lobes (Fig. 5B). The patient continues on cortisone 37.5 mg. daily, sodium chloride 6 gm. daily, streptomycin and PAS and is well, but his incorrigible personality seems forever to prevent him from resuming a useful place in society.

CASE 5. (E.C.). A 51-year-old French Canadian hospital orderly had lost 77 pounds in the year previous to admission and a month before admission showed skin and mucous membrane pigmentation. Serum electrolytes and blood sugar were all normal, the blood pressure was 90/60 and the chest film showed questionably active pulmonary tuberculosis (Fig. 6A). The sputum, however, was positive. He was admitted to hospital in November, 1951, as a case of acute obstructive jaundice and a cholecystectomy performed. The day following operation an acute collapse occurred with an unobtainable blood pressure, a sodium of 130 mEq./L., a chloride of 90 mEq./L. and a potassium of 3.7 mEq./L. He received emergency treatment consisting of adrenal cortical extract, cortisone and intravenous fluids. He responded to therapy and was then maintained on 50 mg. cortisone daily and 6 gm. of NaCl/day. While on this treatment the 17 ketosteroids were 1.5 mg./24 hours, the corticoids 77 Gl.U/24 hours and the electrolytes remained low with a serum sodium of 135 mEq./L., a chloride of 101 mEq./L. and a potassium of 4.85 mEq./L. Streptomycin 1 gm. twice weekly and PAS 12 gm. daily were also instituted at this time. There was clearing of the parenchymal infiltration in the right upper lobe 25 days later (Fig. 6B). In February, there was a sudden onset of fever, dyspnea, chest pain and an unobtainable blood pressure. A roentgenogram showed a right pleural and percardial effusion (Fig. 6C). Therapy as outlined above was continued and the pleural and pericardial effusions disappeared, as did all the symptoms and signs in 4 days (Fig. 6D). He was asymptomatic for several weeks when there was recurrence of fever to 101°, dyspnea and chest pain. The blood pressure fell to 65/0 and the chest roentgenogram again showed gross cardiac enlargement and fluid in the right interlobar fissure (Fig. 7A). Again the symptoms, signs and Roentgen-ray findings disappeared in 4 days on similar therapy (Fig. 7B). He continued well after this episode, was discharged a month later in March, 1952, on the aforementioned dosage of streptomycin, PAS and sodium chloride, but the cortisone was reduced to 37.5 mg./day and a year later, in March, 1953, the streptomycin and PAS were discontinued. In June, 1953, he returned to his work as hospital orderly and finally in January, 1954, the cortisone was reduced to 12.5 mg./day. He has been well with a blood pressure of 90/60 and normal electrolytes. The symptoms of Addison's disease return when cortisone dosage is dropped below 12.5 mg./day.

Results. These are summarized in Table 1. On the above regimen clinical improvement and Roentgen-ray evidence of resolution of the pulmonary lesions occurred promptly with disappearance of the tubercle bacilli from the sputum and gastric washings. The improvement has been maintained for 1 to 3½ years after discontinuance of the streptomycin. Four of the 5 patients are active and carry on a full-time occupation.

The first patient studied (A.A.) was begun on antituberculous therapy 2 weeks after cortisone administration had been initiated. Within 7 weeks there was definite clearing of the infiltration in the left upper lobe. The strep-

tomycin and PAS were discontinued after 8 months' administration. At this time repeated gastric washings were negative on culture and the chest roentgenogram showed clearing of the lesion with residual fibrosis and displacement of the heart and mediastinum to the left. This patient began working in January, 1951, and has continued in good health with no activity of the pulmonary lesion for 3½ years (Fig. 1). It is interesting to note that this patient's hypertension and menses returned 3 months after institution of cortisone therapy.

The second patient (D.P.) had shown no evidence of clearing of the bilateral apical pulmonary tuberculosis after 3 months of supportive sanatorium care prior to his admission in Addisonian crisis. On instituting cortisone, sodium chloride, streptomycin and PAS there was rapid clearing of the apical lesions, particularly on the right, within 6 weeks. The streptomycin was discontinued after 3 months because of blurring of vision, while the remaining therapy was unchanged. In spite of this, Roentgen-ray examination 6 weeks later and 4½ months after institution of therapy showed further clearing of the opacities in the right lung. The cough had disappeared, the sputum was reduced in amount and culture was negative on 3 consecutive days. There was rapid progressive weight gain and the patient has remained well and working since August, 1952 (Fig. 3).

The third patient (Y.L.) had Addison's disease and active pulmonary tuberculosis and was hospitalized at a sanatorium receiving supportive therapy only. The sputum which had been positive initially, became negative on this regimen. Prior to instituting cortisone as replacement therapy, a repeat chest roentgenogram suggested activity in the right upper lobe with a small lesion at the left apex. Physical examination showed fine moist râles over the right apical region, but the sputum was negative. Cortisone, sodium chloride, streptomycin and PAS were begun in October, 1951, with marked clinical improvement. There was clearing of the lesion in the right apex on reexamination 3 weeks later, and he was returned to the sanatorium. One year later streptomycin and PAS were discontinued and the patient was discharged from the sanatorium as arrested (Fig. 4). Cortisone was reduced to 37.5 mg. daily and he has continued in good health. At the present time the maintenance dose of cortisone is 25 mg. per day.

The fourth patient (L.C.) has presented a difficult problem in management because of his social and psychological behavior. This man had a history of arrested pulmonary, osseous and genitourinary tuberculosis, and was admitted in Addisonian crisis. Three sputa were negative on smear and culture before initiation of cortisone therapy, and roentgenogram of the chest showed multiple calcific densities in both upper lobes. Six months later, three sputa were positive on culture and no change had occurred in the chest roentgenogram. The patient refused to come into the hospital for streptomycin and PAS administration, and repeated sputum examinations until December, 1951, were negative. At that time it was discovered that the patient was bringing a friend's sputum for examination, and gastric washings and laryngeal swabs in December, 1951, and January, 1952, were positive on culture. In April, 1952, Rimifon was begun and continued for 4 months without change in the patient's condition. Streptomycin and PAS were begun in July, 1952, and have been continued until the present time. The gastric washings have been negative since January, 1953, and the chest

roentgenogram remains unchanged (Fig. 5).

The fifth patient (E.C.) came to our attention during a postoperative collapse following a cholecystectomy, at which time a diagnosis of Addison's disease was made. Active pulmonary tuberculosis was suspected just prior to operation, and a regimen of cortisone, sodium chloride, streptomycin and PAS was begun. Two months later the patient suddenly developed fever, tachycardia, dyspnea, cyanosis and precordial pain with hypotension, and roentgenogram of the chest revealed a pericardial and right pleural effusion. The symptoms, signs and Roentgen-ray findings disappeared in 4 days and recurred 12 days later only to disappear again in 4 days. The patient returned to sanatorium and remained on the antituberculous therapy for one year. The initial clearing of the roentgenogram which was present after 25 days was maintained and he returned to work as a hospital orderly 3 months later (Figs. 6 and 7). The patient remains well and the cortisone dosage has been gradually reduced to 12.5 mg. per day below which his Addison's disease symptoms return.

Discussion. The evidence presented demonstrated that cortisone may be given in cases of Addison's disease with active pulmonary tuberculosis. All of the patients were treated concurrently by the usual dosage of streptomycin and PAS. The first patient (A.A.) was treated quite by accident. She received cortisone for 2 weeks before the diagnosis of pulmonary tuberculosis was proven. Nevertheless the Addison's disease and the tuberculosis exhibited an excellent response with the addition of streptomycin and PAS. This therapeutic regimen was then used in subsequent cases that presented themselves. On the other hand, one case (L.C.) received cortisone for the first 2 years without benefit of streptomycin and PAS and without spread of the tuberculosis. He too had positive sputa at least for the second of these 2 years, but at no time was there Roentgen-ray evidence of tuberculous spread. It was also the impression of one of the chest physicians of our group, J.F.M., that the pulmonary clearing was more rapid in patients (A.A.) and (D.P.) under the influence of cortisone than one would normally anticipate in such cases using streptomycin and PAS alone.

Cortisone was used in 50-mg. daily doses initially but the maintenance daily dose for these patients varies between 12.5 and 37.5 mg. This is probably the physiologic replacement. It does not compare with the larger nonphysiologic doses used in the treatment of such diseases as arthritis and asthma. The administration of a physiologic dose may account for the beneficial effect of the cortisone on the existing tuberculosis. Sodium chloride supplement has been in the order of 6 gm. per day. This has been sufficient in our hands. To date we have not found it necessary to add desoxycorticosterone to this regimen, although the cases have been followed for 3 to 5 years.

The etiology of the acute pericardial and pleural effusions in E.C. is undetermined, but several possibilities exist. It could conceivably have been of a tuberculous nature but the rapid clearing would tend to discredit this view. However, we have never before observed the behavior of tuberculous pericarditis and pleuritis while on cortisone, streptomycin and PAS. The other possibility is that the pericarditis and pleuritis were of viral origin.

Summary. 1. Five patients with Addison's disease and active pulmonary tuberculosis have been treated with streptomycin, PAS and isonicotinic acid while being maintained on cortisone

acetate and supplementary sodium chloride.

2. Clinical improvement and Roentgen-ray evidence of resolution of the pulmonary lesions occurred promptly with the disappearance of the acid-fast organisms from the sputum and gastric washings.

3. Improvement has been maintained for 1 to 3½ years after cessation of active antituberculous therapy while cortisone acetate and sodium chloride have been continued. Four of the 5 patients are active and carrying on a full-time occupation.

4. Cortisone acetate in replacement dosage in Addison's disease when combined with antituberculous therapy seems to be the treatment of choice in these patients.

5. Spread of pulmonary tuberculosis on this dosage of cortisone acetate has not occurred.

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THE INCIDENCE OF PERFORATION IN BENIGN PEPTIC ULCER OF THE GREATER CURVATURE OF THE STOMACH

By Maurice Feldman, M.D.
BALTIMORE, MARYLAND

There has been a dearth of statistical data concerning perforation of benign peptic ulcers situated on the greater curvature of the stomach. A survey of the literature on this subject revealed that most of the reports are case records of but 1 or 2 cases. It seemed that more objective information needs to be collected on certain aspects of greater curvature ulcerations. The purpose of this paper is therefore fourfold. (1) To determine the incidence of benign peptic ulcer situated on the greater curvature of the stomach. (2) To determine how often these ulcers perforate. (3) To note the site of perforation. (4) To determine what organs and adjacent tissues are involved. In addition to this study, the literature was reviewed and 68 collected cases were compiled in order to obtain data necessary to determine the incidence of perforation of benign peptic ulcer of the greater curvature.

Although there is a relative low incidence of occurrence of benign peptic ulcers on the greater curvature of the stomach, this incidence is probably greater than has hitherto been believed. Collected reports of the incidence varies from 0.5 to 14% of all ulcers. The latter figure seemed to be unusually high. However, the true incidence more likely approximates from 2 to 3%. The recorded incidences of benign gastric ulcers of the greater curvature are shown in Table 1.

It was formerly believed that most peptic ulcers occurring on the greater curvature were due to some specific cause, and that the majority of these were malignant. In recent years, it has been shown that this assumption is not true, and that many of these ulcers are definitely benign. It has been found that from 35 to 50% are benign. Boudreau[2], who reported 234 necropsied cases of gastric ulcer, found 47 involving the greater curvature, of which 24 or 51% were benign.

The ulcerations on the greater curvature are situated chiefly in the body. Of the 68 collected cases, the exact site was mentioned in 58. The sites of the ulcer are shown in Table 2. The incidence of the site of the benign pep-

TABLE 1.—INCIDENCE OF BENIGN PEPTIC ULCER OF THE GREATER CURVATURE

	Number of Gastric Ulcer Cases			*Number of Cases of Greater-Curvature*	
Author	*Necropsy*	*Clinical*	*Surgical*	*Ulcer*	%
Gott *et al.*[4]		162		3	1.85
Palmer[5]		100		9	9.0
Portis and Jaffe[7]	196			1	0.5
Smith and Jordan[9]			211	2	1.0
Baker and Gattas[1]			119	4	3.3
Welch and Allen[10]			512	6	1.2
Lorenz[6]			1,357		3.8
Boudreau *et al.*[2]	168			24	14.0
Sladky[8]			128	1	0.8

tic ulcer on the greater curvature of the stomach is presented in Fig. 1. Of the 12 perforated ulcer cases, the site was mentioned in 7 instances as follows: 4 in the body, 2 in the antrum, and 1 in the prepylorus.

TABLE 2.—SITE OF THE ULCER ON THE GREATER CURVATURE

Location of the Ulcer	*Author*	*Baker and Gattas*[1]	*Palmer*[6]
Cardia		1	
Fundus		1	
Pars Media (Body)	29	17	3
Antrum	15	3	
Prepylorus	14	10	6
Pylorus		1	
Total Cases	58	33	9

sizes of the ulcer in the 29 cases are shown in Table 3.

TABLE 3.—THE SIZE OF THE ULCER IN 29 CASES

Size of Ulcer, cm.	*Number of Cases*	*Size of Ulcer, cm.*	*Number of Cases*
0.5	1	3.2	1
1.0	3	3.5	1
1.5	5	4.0	3
2.0	4	4.5	0
2.2	1	5.0	3
2.5	3	5.5	1
3.0	3		

Multiple ulcers are not commonly observed on the greater curvature. In the 68 collected cases multiple ulcerations were mentioned in only 3 instances; 2 of these revealed 2 ulcers, and in one case there were 3 ulcers. In Baker and Gattas' 33 collected cases[1], 4 instances of multiple ulcers were observed.

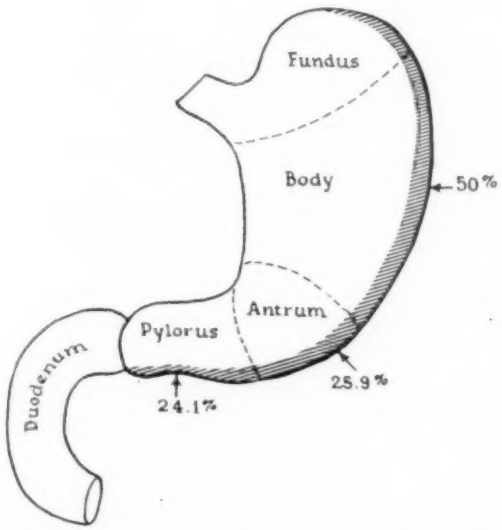

Fig. 1.—Shows the incidence of the site of benign peptic ulcer on the greater curvature of the stomach in 58 cases.

The size of the ulcers ranged from 0.5 to 5.5 cm. in diameter. In 29 of the 68 collected cases in which the size of the ulcer was given, the average size was 2.6 cm. It is of interest to point out that the average size of the greater-curvature ulcers is larger than those occurring on the lesser curvature. The

It is noteworthy to mention that greater-curvature ulcerations are not generally associated with benign pep-

tic ulcers elsewhere in the stomach and duodenum. In the 68 collected cases, there were 2 instances of the association of a peptic ulcer on the lesser curvature and 5 with duodenal ulceration, of which 2 were healed. In Baker and Gattas' 33 collected cases, there was only one instance of an associated peptic ulcer on the lesser curvature and 4 with a duodenal ulcer.

In a perusal of the literature the impression is gained that perforations of peptic ulcers of the greater curvature of the stomach occur with greater frequency than in ulcers on the lesser curvature. In the 68 collected cases of benign peptic ulcer of the greater curvature, there were 12 instances of perforation, an incidence of 17.6%. This incidence is considerably higher than the incidence of perforation of lesser-curvature ulcers. However, the true incidence may not be so high, because only the surgically explored and necropsied cases were recorded, while probably a larger number of cases have not been reported. On the other hand, there have been too few cases to establish accurately the incidence of perforation of greater-curvature ulcers.

There are very few references in the literature which give the incidence of perforation of benign peptic ulcers situated on the greater curvature of the stomach. In 500 cases of gastroduodenal perforations reported by Corvese *et al.*[3], 167 were gastric, and of these, only 4 involved the greater curvature, an incidence of 2.4%.

Deserving of comment and worthy of more emphasis is the fact that when greater-curvature ulcers perforate, they rarely involve the greater or lesser peritoneal cavities, but are more apt to involve the adjacent viscera or tissues.

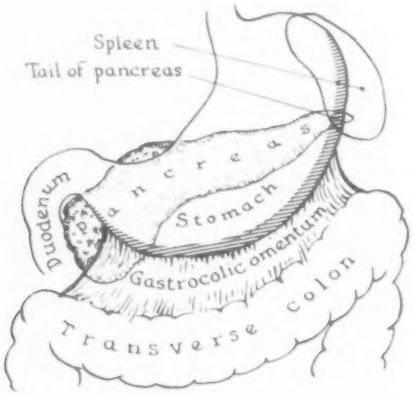

Fig. 2.—Illustrates the anatomic relationship of the spleen, tail of the pancreas, gastrocolic omentum, and transverse colon, with the greater curvature of the stomach.

TABLE 4.—THE VISCERA INVOLVED IN PERFORATION OF BENIGN PEPTIC ULCER OF THE GREATER CURVATURE

Viscera Involved	*Cases*
Perforation into Greater Peritoneal Cavity	1
" " Lesser Peritoneal Cavity	0
" " Gastrocolic Omentum	4
" " Transverse Colon	2
" " Spleen	3
" " Pancreas	1
" " Liver	1
Total Cases	12

In the 12 perforated cases, there was only one instance of perforation involving the greater peritoneal cavity, and

none involved the lesser peritoneal cavity. In 2 instances the ulcer perforated into the transverse colon, producing a gastrocolic fistula. In 4 cases involving the gastrocolic omentum, all of these perforations were of the walled-off type. The anatomic relationship of the greater curvature of the stomach to the adjacent viscera is shown in Fig. 2. It lies adjacent to the gastrocolic omentum, transverse colon, spleen, and the tail of the pancreas. The structures involved in the perforations of 12 cases are shown in Table 4.

The sex incidence is almost equal. In 41 of the 68 cases in which the sex was mentioned, there were 24 males and 17 females.

The ages of 43 of the 68 collected cases ranged from 23 to 74 years. Over half of the cases occurred in the 5th and 6th decades. There were 4 in the second, 6 in the third, 7 in the fourth, 13 in the fifth, 12 in the sixth, and 1 in the seventh decades.

Conclusions. (1) The incidence of benign peptic ulcer of the greater curvature of the stomach is approximately 2 to 3% of all such ulcers.

(2) Benign peptic ulcers of the greater curvature occur predominantly in the body of the stomach (50%).

(3) The average size of the greater-curvature ulcers is larger than that of those occurring on the lesser curvature. The average diameter of the ulcer in 29 cases was 2.6 cm.

(4) Benign peptic ulcers of the greater curvature are not generally associated with peptic ulcers elsewhere in the gastroduodenal region. Of the 68 cases, there were 7 instances (10%) with associated lesser-curvature or duodenal ulcerations.

(5) In 68 collected cases of benign peptic ulcer of the greater curvature, there were 12 instances of perforation, an incidence of 17.6%.

(6) Of the 12 perforated peptic ulcer cases, 11 perforated into the adjacent viscera. The gastrocolic omentum, transverse colon, and spleen were most commonly involved.

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THE EFFECT OF AGE ON THE PROTEIN CONCENTRATION OF CEREBROSPINAL FLUID OF "NORMAL" INDIVIDUALS AND PATIENTS WITH POLIOMYELITIS AND OTHER DISEASES*

By Otto H. Müller, R.N.Dr.
ASSOCIATE PROFESSOR OF PHYSIOLOGY

Alexander A. Jaworski, M.D.
FELLOW IN PHYSIOLOGY AND ASSISTANT RESIDENT IN PEDIATRICS

A. Clement Silverman, M.S., M.D.
CLINICAL PROFESSOR OF PEDIATRICS

AND

Mary Jane Elwood, B.S.
RESEARCH ASSISTANT IN PHYSIOLOGY

(From the Departments of Physiology and Pediatrics, State University of New York, Upstate Medical Center College of Medicine, Syracuse, New York)

The determination of protein in cerebrospinal fluid (CSF) has become a major aid in the diagnosis of poliomyelitis and a number of other diseases. It has been well established that a normal protein concentration along with an elevated cell count of the CSF may be expected at the onset of poliomyelitis. During the second or third week of the disease, the picture reverses and the cell count is on its way to normal while the protein concentration is increasing towards a peak value. In general, a protein concentration of less than 40 or 45 mg. per 100 cc. is taken as a normal value[2,4,5]. In the City Hospital of Syracuse, from which most of our specimens and diagnoses came, the criterion for normalcy was 20 to 40 mg. protein per 100 cc. and less than 10 cells per cubic millimeter.

For purposes of a polarographic study[6], we determined the protein concentration of all CSF samples obtainable during the study period. These came from patients with poliomyelitis and with central nervous system involvement other than poliomyelitis, as well as from supposedly normal individuals** and from poliomyelitis follow-up patients. Since there was a considerable spread in the age of the CSF donors in each group, it was possible to make the analysis presented here, showing a definite effect of age on the concentration of protein in CSF. This effect, which apparently has not been recognized before, is slight in "normal" individuals but becomes very marked in patients with poliomyelitis and diminishes again when these patients have recovered from the disease.

Methods. PROTEIN ANALYSIS. The protein determinations were carried out with a Klett-Summerson colorimeter, according to directions given with the instrument, which seems to be a modification of the method of Denis and Ayer[3]. The protein contained in 1 cc. of CSF was precipitated with 4 cc. of 3% sulfosalicylic acid. The resulting precipitate was so fine that it did not settle out during the period of observation. Its light absorption

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**Individuals with no disease or with diseases or defects which, as far as is known, do not alter the composition of CSF.

was measured after 10 minutes with the aid of a blue filter (No. 42). A standard curve was obtained by averaging results obtained with several normal sera with known protein contents which had been suitably diluted with 15% sodium chloride solution. A linear relationship was found between colorimeter readings and protein concentration up to 125 mg. protein per 100 cc. and the line went through the origin.

The CSF samples were centrifuged, if necessary, and analyzed within 24 hours after collection; up to the time of analysis they were kept in a refrigerator. Nearly all of the specimens were free from erythrocytes. Certainly all "normal" samples satisfied this criterion. However, in the various diseases with elevated CSF protein only samples containing 5,000 erythrocytes per cubic millimeter, or more, were rejected. This seemed justifiable, in view of the following considerations and experiments, as long as the sample was centrifuged and analyzed before any hemolysis could take place.

TABLE 1.—EFFECT OF TRACES OF WHOLE BLOOD ON THE PROTEIN ANALYSIS OF CEREBROSPINAL FLUID

	Sample A		*Sample B*		*Sample C*	
	Cells mm.³	*Protein mg./100 cc.*	*Cells mm.³*	*Protein mg./100 cc.*	*Cells mm.³*	*Protein mg./100 cc.*
Original CSF	50	9	0	25	0	19
plus traces of whole blood						
not centrifuged	8000	33	1500	34	4000	61
centrifuged	0	18	0	26	0	42

TABLE 2.—EFFECT OF STORAGE IN A REFRIGERATOR ON CSF WITH AND WITHOUT A TRACE OF WHOLE BLOOD

		CSF plus Trace of Whole Blood			
		Not Centrifuged		*Centrifuged*	
Date	*Cell-free CSF Protein mg./100 cc.*	*Cells mm.³*	*Protein mg./100 cc.*	*Cells mm.³*	*Protein mg./100 cc.*
1/2/51	16	2400	27	0	20
1/3/51		2200	28	0	21
1/4/51		2000	33	0	22
1/5/51		640	40	0	38
1/9/51	16				
1/10/51	16	0	40	0	39

TABLE 3.—EFFECT OF CENTRIFUGATION AND HEMOLYSIS ON PROTEIN ANALYSIS OF CEREBROSPINAL FLUID CONTAINING TRACES OF WHOLE BLOOD

Date of Analysis		1/3/51 *Not Centrifuged No Hemolysis*	1/3/51 *Centrifuged No Hemolysis*	1/10/51 *Not Centrifuged Hemolysis*
	Cells mm.³*	*Protein mg./100 cc.*	*Protein mg./100 cc.*	*Protein mg./100 cc.*
(a) Original CSF	0	16	16	16
(b) CSF plus trace of blood	2200	28	21	37
(c) " " " " "	220	17	16.5	24
(d) " " " " "	22	16.5	16.5	23

* (a) and (b) determined by direct count.
(c) and (d) obtained by 10- and 100-fold dilution of (b) with (a).

Effect of traces of whole blood on protein analyses of CSF. It can be calculated that the presence of 5,000 erythrocytes per cubic millimeter means the addition of 0.001 cc. of normal blood to each cc. of CSF, hence also a probable addition of 6 mg. *plasma* protein per 100 cc. This was tested by sev-

eral experiments with results shown in Table 1. It is obvious from this that unless the erythrocytes are removed by centrifugation, they are also precipitated by the sulfosalicylic acid and thus contribute to the light absorption. The analyses of the supernatants, after centrifugation, are in good agreement with the above calculation in samples A and B. The discrepancy in sample C may have been caused by hemolysis. A more detailed study of this effect was consequently carried out. The results, given in Tables 2 and 3, indicate that centrifugation is no longer of value, once hemolysis has started. They further show that the effect of centrifugation becomes less pronounced as cell count decreases, even if the sample is fresh and not hemolyzed. Note that even small traces of admixed blood can cause appreciable errors after hemolysis of the erythrocytes. A further experiment was carried out to see the effect of storage at room temperature and in the refrigerator on two sterile, cell-free CSF specimens with protein concentrations of 25 and 135 mg. per 100 cc. No change was found for either sample if stored for a week in the refrigerator, but measurable, although not large, changes were produced in that time at room temperature. Of interest was the observation that even 2 or 3 days' storage at room temperature resulted in no measurable changes, so that possible warming of our samples during transport from hospital to laboratory should be without effect on our results.

Sample Material. For the clinical material we are indebted to the staffs of City Hospital, Memorial Hospital, and University Hospital, and in particular to Drs. Severance, Ecker, Batkin, and Delmonico.

The data presented here are based on a study of CSF samples taken during the season of 1950-1951. During this time there was an epidemic of poliomyelitis in the Syracuse area[7] with 334 cases reported, of which 273 could be included in our study. A small fraction of our data had been accumulated during the preceding year in a preliminary study. We were also able to secure CSF specimens from 37 follow-up cases who had had poliomyelitis more than 31 days before the last spinal puncture. In two of these volunteers, a period of 34 years had passed since their attack of paralytic poliomyelitis.

Patients, or parents of child patients, have an understandable hesitancy in permitting a renewed spinal puncture for research purposes. We consider ourselves quite fortunate in getting a fair number of volunteers for this and wish to express our gratitude to them here for their contribution.

Along with the poliomyelitis cases came 175 cases of respiratory infections and "non-meningeal" cases, many of which had come to the hospital with a suspicion of poliomyelitis. Also 31 cases of meningitis and 47 cases of other involvement of the central nervous system were included. When our studies showed the need for more "normal" CSF values, we secured sufficient sample material from 121 preoperative cases during spinal anesthesia.

Our results made it expedient to segregate our sample material into the groups as shown on Page 513.

Naturally the CSF samples in our poliomyelitis cases had to be taken whenever possible. Hence they are not strictly comparable since the time of sampling, listed as "day after onset" of the disease (DAO),* may vary from case to case. To minimize any bias, we included in our statistical analysis only the first CSF specimens obtained from any one patient during the first 21 days after onset of the disease. Out of 51 cases in which the repeated spinal taps were made within 40 DAO, this procedure yielded 28 values which were higher and 23 values which were lower than subsequent values. Out of 19 cases in which a second spinal tap was made more than 100 DAO, the first sample yielded uniformly the higher value. About 88%

*In cases in which the disease has a biphasic onset, the first day of the second phase was considered as the "day of onset."

	No. of Cases		
POLIOMYELITIS:			
Paralytic poliomyelitis	150		
Nonparalytic poliomyelitis	105		
Bulbar poliomyelitis	25		
Bulbospinal poliomyelitis	19		299
FOLLOW-UPS: (Disease contracted more than 31 days ago)			
Paralytic poliomyelitis	26		
Nonparalytic poliomyelitis	5		
Bulbospinal poliomyelitis	6		37
"NORMALS":			
Respiratory infections:			
Pharyngitis	62		
Pneumonia	11		
Tonsillitis	19		
Upper respiratory infection	8	100	
Preoperative Cases:			
Hernia	31		
Appendicitis	20		
Cholecystitis	17		
Hemorrhoids	10		
Cancer	10		
Miscellaneous diseases and defects requiring surgery	33	121	
"Nonmeningeal" Cases			
Myositis	9		
Infectious mononucleosis (Without C.N.S. involvement)	8		
Myalgia	6		
Pulmonary tuberculosis	4		
Miscellaneous diseases not known to alter the CSF*	32		
Cases in which no definite diagnosis could be made or in which the patient was considered disease-free	16	75	296
"C.N.S.-INVOLVEMENT":			
Epilepsy		8	
Mumps encephalitis		6	
Infectious neuronitis		5	
Subarachnoid hemorrhage		4	
Mental retardation		3	
Miscellaneous C.N.S. disturbances**		21	47
MENINGITIS:			
Influenzal meningitis		9	
Meningococcal meningitis		8	
Pneumococcal meningitis		6	
Tuberculous meningitis		3	
Meningitis with questionable etiology		3	
Streptococcal meningitis		1	
Chronic arachnoiditis		1	31

*For example, scarlet fever, sinusitis, stomatitis, torticollis, serum sickness, arteriosclerosis, abscess, anemia, bursitis, chickenpox, cystitis, dysentery, enteritis, mumps (without C.N.S. involvement), lymphadenitis, pertussis, rheumatic fever, rheumatoid arthritis, otitis media, osteomyelitis, and others.

**For example, cerebral atrophy, contusion, hemorrhage, thrombosis, abscess; metastatic carcinoma; hydrocephalus; neurosyphilis; alcoholic and diabetic neuritis; psychosis; psychoneurosis; and others.

TABLE 4.—PROTEIN CONTENT OF CEREBROSPINAL FLUID IN RELATION TO AGE IN DIFFERENT TYPES OF POLIOMYELITIS

	Paralytic			*Nonparalytic*			*Bulbar*			*Bulbospinal*			*All Types*		
Age Group	*No. of Cases*	*Range mg./100 cc.*	*Mean mg./100 cc.*	*No. of Cases*	*Range mg./100 cc.*	*Mean mg./100 cc.*	*No. of Cases*	*Range mg./100 cc.*	*Mean mg./100 cc.*	*No. of Cases*	*Range mg./100 cc.*	*Mean mg./100 cc.*	*No. of Cases*	*Range mg./100 cc.*	*Mean mg./100 cc.*
0–4	47	18–117	48.1	22	17–79	42.4	4	24–35	29.5	4	41–78	52.3	77	17–117	45.7
5–9	34	25–122	59.0	22	25–92	51.3	12	28–96	51.8	2	35–48	41.5	70	25–122	54.8
10–14	21	29–130	72.8	14	32–91	62.6	4	38–70	47.0	4	61–80	68.0	43	29–130	66.7
15–19	10	32–132	76.6	15	29–138	76.4	2	48–92	70.0	3	50–126	90.3	30	29–138	77.4
20–24	11	23–275	88.6	18	38–117	74.0							29	23–275	79.6
25–29	8	61–118	108.6	7	42–209	99.3	3	52–175	108.0	3	43–92	67.0	21	42–206	99.5
30–34	7	43–154	85.4	3	37–65	55.7				2	148–170	159.0	12	37–170	90.3
35–39	8	28–175	79.5	3	65–114	93.0				1		118.0	12	28–175	86.1
40–44	2	45–320	182.5	1		156							3	45–320	173.7
45–49	2	94–154	124.0										2	94–154	124.0
Total	150	18–320	68.3	105	17–209	63.9	25	24–175	55.7	19	35–170	77.5	299	17–320	66.3

TABLE 5.—PROTEIN CONTENT OF CEREBROSPINAL FLUID OF "NORMALS" IN RELATION TO AGE

	"Nonmeningeal"			*Preoperative*			*Respiratory Infections*			*All "Normals"*		
		Protein, mg./100 cc.			*Protein, mg./100 cc.*			*Protein, mg./100 cc.*			*Protein, mg./100 cc.*	
Cases Age	*No. of Cases*	*Range*	*Mean*	*No. of Cases*	*Range*	*Mean*	*No. of Cases*	*Range*	*Mean*	*No. of Cases*	*Range*	*Mean*
0–4	20	15–50	27.6				31	15–38	22.4	51	15–50	24.4
5–9	12	9–45	22.1	1		35	29	10–37	24.1	42	9–45	23.3
10–14	8	18–46	28.0				14	11–52	26.1	22	11–52	26.8
15–19	7	13–34	25.9	5	26–37	30.6	7	23–30	26.6	19	13–37	27.4
20–24	8	26–50	36.4	9	29–38	33.1	8	19–44	28.9	25	19–50	32.8
25–29	5	22–57	38.2	9	28–80	39.9	2	33–62	47.5	16	22–80	40.3
30–34	1		31	13	19–70	41.3	6	29–65	41.5	20	19–70	40.9
35–39	4	23–35	30.8	21	22–84	40.6				25	22–84	39.0
40–44	4	31–130	62.5	18	30–74	45.4				22	30–130	48.5
45–49				11	19–91	36.2				11	19–91	36.2
50–54	2	18–44	31.0	8	20–91	38.8	1		77	11	18–91	40.8
55–59	2	18–39	28.5	10	35–91	53.3				12	18–91	49.2
60–64	1		135	4	36–96	56.0				5	36–135	71.8
65–69				8	13–65	35.8				8	13–65	35.8
70–74				3	18–44	33.7				3	18–44	33.7
75–79	1		46	1		50	2	19–22	20.5	4	19–50	34.3

of the analyses deal with samples obtained within 7 DAO, while almost 99% deal with samples obtained within 14 DAO.

Results. POLIOMYELITIS. The data obtained on the poliomyelitis cases are summarized in Table 4. In general, there seems to be no difference between the four different types of poliomyelitis. They all show the same marked increase in the protein concentrations with age. This is more clearly brought out in the graphic analysis of the mean values for the different age groups shown in Fig. 1.

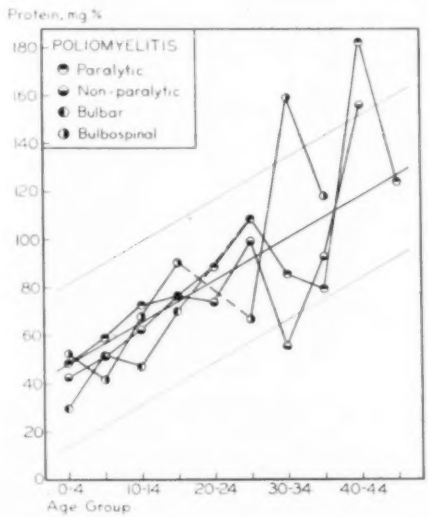

Fig. 1

Since such graphs are not entirely reliable, especially in the region where the "mean" values represent only one or two cases, we have made a statistical analysis of our results, which has been summarized in Table 8 along with other statistics. In columns 2 and 3 of this table, the data obtained on 150 paralytic and 105 nonparalytic poliomyelitis cases are compared. The results are strikingly similar, which may be taken as a confirmation of the diagnoses of nonparalytic poliomyelitis. The slopes of the protein-age curves are of the same magnitude and they are highly significant, with t values in excess of 6. The following equations, in which the protein concentration is given in mg. per 100 cc. and the age in years, will hold for the two types of poliomyelitis:

Paralytic Poliomyelitis: CSF Protein $= 47.3 + 1.66 \times$ Age $\pm$ 39.0 (1)

Nonparalytic Poliomyelitis: CSF Protein $= 40.2 + 1.71 \times$ Age $\pm$ 26.0 (2)

In view of the uniformity of these two major groups of poliomyelitis and the similar trend of the two others, all the poliomyelitis cases were grouped together, as shown in Table 4 and column 4 of Table 8. The t value of the regression curve is now in excess of 9 and the equation for the curve is:

Poliomyelitis CSF Protein $= 43.0 +$ $1.77 \times$ Age $\pm$ 33.7 (3)

The regression line for the 299 poliomyelitis cases has been drawn in Fig. 1 along with two parallel lines indicating the range of $\pm$ 1 standard deviation.

"NORMALS". The data obtained on the "normal" cases are summarized in Table 5. Here, too, there seems to be

no difference between our three subgroups. They all show a small but definite increase in the protein concentration with age, which is clearly brought out in the graphic representation of the mean values for the different age groups shown in Fig. 2. The cases with respiratory infections were younger than the preoperative cases which had more representation in the older-age groups. This may account for some of the difference brought out between the groups when the results are analyzed statistically, as in Table 8, columns 5 to 7. The slopes for the respiratory infection and nonmeningeal cases are somewhat steeper than the slope for the preoperative cases. However, the latter is barely significant with a t value of 1.929. When all three groups are combined, as in Table 5 and in column 8 of Table 8, an intermediate slope is found which, with a t value of more than 9 is as significant as the slope for the poliomyelitis cases.

The following equation holds for the combined "Normals":

$$\text{Normal CSF Protein} = 23.8 + 0.39 \times \text{Age} \pm 15.0 \qquad (4)$$

The regression line for the 296 "normal" cases has been drawn in Fig. 2, along with two parallel lines indicating the range of $\pm$ 1 standard deviation.

CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT. The number of patients (47) with CNS involvement was relatively small and the group was probably not homogeneous enough to warrant serious consideration. The results are summarized in Table 6 and the statistical data are given in column 9 of Table 8. The latter indicate a slightly greater effect of age on the protein concentration than "normal." Judging from the t value of 2.514, this effect is significant.

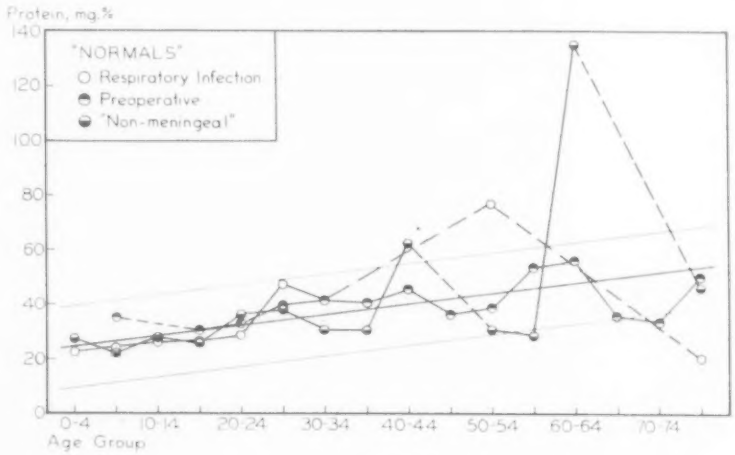

Fig. 2

MENINGITIS. The 31 cases of meningitis were not expected to yield much information about the effect of age on the concentration of protein in CSF, since the latter changes very rapidly depending on the intensity of the disease. The data summarized in Table 6 serve to illustrate the tremendous range of values, and the high mean values which are characteristic of the disease.

FOLLOW-UP POLIOMYELITIS CASES. Results obtained with follow-up cases are

summarized in Table 7. In general, they seem to approach "normal" values. However, the statistical data in column 10 of Table 8 show a t value of 2.816, which indicates that the slope of the curve is not quite significant. This is understandable, since in the arbitrary choice of 31 DAO for all follow-up cases undoubtedly some cases were included in which the disease was still

proach to normalcy. Note that nearly all of these means fall inside the ± 1 standard deviation range. The one notable exception is caused by a CSF (117 mg. per 100 cc. protein) which was obtained 105 DAO from a 34-year-old respirator patient suffering from bulbospinal poliomyelitis.

It would be interesting to know to what extent a past history of polio-

TABLE 6.—PROTEIN CONTENT OF CEREBROSPINAL FLUID IN RELATION TO AGE OF PATIENTS WITH "CENTRAL NERVOUS SYSTEM INVOLVEMENT" AND WITH MENINGITIS

Cases	*C. N. S. Involvement*			*Meningitis*		
		Protein, mg./100 cc.			*Protein, mg./100 cc.*	
Age	*No. of Cases*	*Range*	*Mean*	*No. of Cases*	*Range*	*Mean*
0–4	12	15–128	41.8	16	22–350	179.2
5–9	10	22–84	44.2	5	22–450	142.6
10–14	3	17–26	20.7	2	68–414	241.0
15–19	2	35–58	45.5	1		131
20–24	1		50			
25–29						
30–34	2	47–68	57.5	2	110–175	142.5
35–39						
40–44	2	43–78	60.5	1		37
45–49	4	13–112	50.0			
50–54				1		775
55–59	4	19–150	74.3			
60–64	5	30–218	108.0	1		414
65–69	1		24	1		500
70–74	1		32			
75–79						
80–84				1		80

TABLE 7.—PROTEIN CONTENT OF CEREBROSPINAL FLUID IN RELATION TO AGE OF PATIENTS WHO HAD CONTRACTED POLIOMYELITIS MORE THAN 31 DAYS AGO

		Protein, mg./100 cc.	
Age	*No. of Cases*	*Range*	*Mean*
0–4	15	13–43	24.9
5–9	13	15–83	37.2
10–14	1		26
15–19	4	31–54	42.8
20–24	1		39
25–29	2	30–44	37
30–34	2	39–117	78
35–39	2	34–61	47.5
40–44	1		34

active. The mean values of Table 7 have been plotted in Fig. 3 along with the mean values for all "normals" taken from Table 5, to illustrate this ap-

myelitis contributes to the small but definite increase in the protein concentration of the CSF of "normals." Unfortunately, our data do not permit us to give a definite answer to this question. It is our impression, however, that the increase of CSF protein with age in normals has no relationship to poliomyelitis or to acquired immunity to the disease. This guess is based on the finding that out of 25 patients whose CSF protein we determined during the acute phase of the disease and then again later at times varying from 105 DAO to 294 DAO, only 3 failed to have final values within ± 1 standard deviation from "normal." Furthermore,

the two volunteers who had paralytic poliomyelitis more than 34 years ago had CSF protein values in perfect agreement with the "normal" curve. If the normal curve was the result of a mixture of elevated values for recovered poliomyelitis patients and lower values for true normals, we feel we would have found more values higher than the 1 standard deviation from normal in these late follow-ups.

COMPARISON WITH LITERATURE DATA. In our search of the literature, we have found only one compilation of data which we could use for comparison with our work. A paper by Andelman, Fishbein, Casey and Bundesen[1] contained all the information needed by us, such as protein concentration, age of the patient, disease, and date of on-

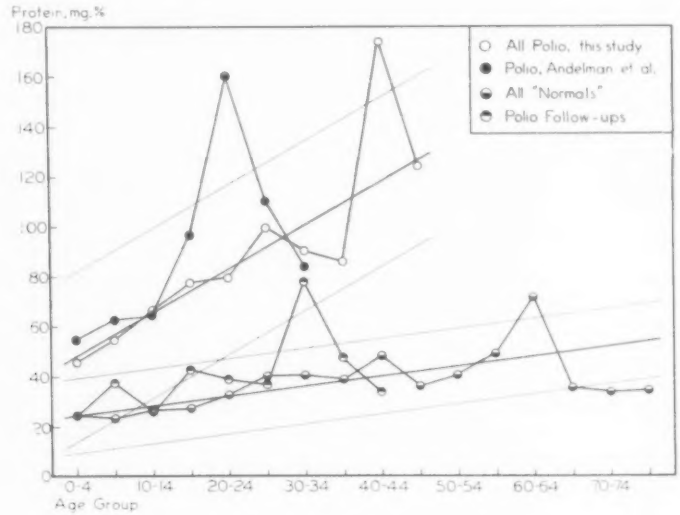

Fig. 3

TABLE 8.—STATISTICAL DATA*

Relationship between Age (X) and CSF Protein Concentration (Y)

	Paralytic Poliomyelitis	*Non-paralytic Poliomyelitis*	*All Poliomyelitis*	*"Non-meningeal"*	*Preoperative*	*Respiratory Infection*	*All "Normals"*	*C.N.S. Involvement*	*Poliomyelitis Follow-Ups*	*Andelman et al. Poliomyelitis*
n	150	105	299	75	121	100	296	47	37	70
ΣX	1925	1460	3944	1356	5094	1187	7637	1197	444	608
ΣX^2	45365	29778	85874	47092	240414	31939	319445	57957	10056	7772
$\bar{x}$	12.833	13.905	13.191	18.080	42.099	11.870	25.801	25.468	12.000	8.686
Σx^2	20661	9477	33850	22576	25961	17849	122405	27472	4728	2491
ΣY	10295	6713	19838	2405	4954	2637	9996	2476	1340	4681
ΣY^2	989109	526343	1758506	105594	235892	80727	422168	210696	63726	386525
$\bar{y}$	68.633	63.933	66.348	32.067	40.942	26.370	33.770	52.681	36.216	66.871
Σy^2	282529	97159	442298	28474	33065	11189	84600	80258	15196	73500
ΣXY	166443	109507	321476	54759	213663	36825	305247	79540	19723	46949
Σxy	34324	16164	59800	11277	5104	5524	47343	16481	3643	6291
b	1.661	1.706	1.767	0.500	0.197	0.310	0.387	0.600	0.771	2.525
s_b	0.272	0.267	0.183	0.118	0.102	0.074	0.043	0.239	0.274	0.583
t	6.118	6.388	9.656	4.244	1.929	4.205	9.016	2.514	2.816	4.331
$S_{y.x}$	39.04	25.99	33.66	17.69	16.40	9.83	15.02	39.54	18.79	29.10

* Terms used in accordance with directions given in G. W. Snedecor "Statistical Methods" 4th Ed., Iowa State College Press, 1946, pp. 118–122.

set. This enabled us to carry out a statistical analysis on 70 of their poliomyelitis cases. The results of this are given in column 11 of Table 8. Although their data are not strictly comparable with ours, since their method of protein analysis was not identical, a striking similarity of the results is obvious. This is brought out further in Fig. 3, where the mean values of Andelman *et al.*[1] are plotted along with the mean values of our combined poliomyelitis cases (taken from Table 4). The regression curve for our poliomyelitis cases and the two limiting parallel lines (drawn at ± 1 standard deviation) are also drawn and show that all but one value of Andelman *et al.* fall within these limits. The one exception is not a mean value at all but represents a single value, a CSF protein concentration of 160 mg. per 100 cc. found in a case of paralytic poliomyelitis, 21 years old, tapped 11 DAO. It was the highest value of the whole series of analyses of Andelman *et. al.*[1].

Conclusion. Figure 3 serves to illustrate the following conclusions:

1) The usually accepted value of 40 to 45 mg. per 100 cc. for the concentration of protein in CSF is somewhat on the high side for very small infants and children, and it is probably best for adults of all ages. However, the data shown indicate that values up to 60 mg. per 100 cc. should not be surprising for normal individuals after age 60.

2) In infants and children the ranges of protein concentrations, as indicated by ± 1 standard deviation overlap for the normal and poliomyelitis groups. Hence, the protein concentration in CSF is of minimum value for diagnostic purposes in this group.

3) Above the age of 20 the above two ranges separate more and more so that the diagnostic value of the protein concentration of CSF should become greater for the older person.

Summary. There is a definite increase in the protein concentration of cerebrospinal fluid with age. This increase is slight in normal individuals but is very marked in patients with poliomyelitis. These relationships can be expressed by the following equations (protein concentration in mg. per 100 cc., age in years):

Poliomyelitis CSF Protein $= 43.0 + 1.77 \times \text{Age} \pm 33.7$

Normal CSF Protein $= 23.8 + 0.39 \times \text{Age} \pm 15.0$.

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AN EVALUATION OF THE ANAMNESTIC SERUM REACTION IN CERTAIN FEBRILE ILLNESSES*

By Jacob Koomen, Jr., M.D.
INSTRUCTOR OF BACTERIOLOGY AND MEDICINE

AND

Herbert R. Morgan, M.D.
PROFESSOR OF BACTERIOLOGY AND ASSOCIATE PROFESSOR OF MEDICINE

(From the Laboratories of the Rochester Health Bureau; and the Department of Bacteriology, University of Rochester School of Medicine and Dentistry, Rochester, New York)

It is frequently said that febrile conditions produce a nonspecific increase in typhoid agglutinins in the serum of persons who have been inoculated with typhoid vaccine[5]. Since a rise in typhoid antibody is serologic evidence for infection with the typhoid bacillus in the uninoculated person, in an immunized individual such an increase presents difficulties in interpretation. This is rendered more complex by the fact that inoculation with typhoid vaccine produces only a relative immunity and many persons so immunized have contracted the disease and thus have serum antibodies present at the time of onset of their disease[3].

On examination of the evidence it appears far from established, however, that such rises in typhoid agglutinins regularly occur in febrile illnesses in persons inoculated with typhoid vaccine. Conradi and Bieling[1] noted an increase in titer of typhoid antibody of as much as three-fold in typhoid-immunized patients studied during the course of nonenteric febrile illnesses. It is of interest that Conradi and Bieling first used the term "anamnestic serum reaction" to indicate a recall of typhoid antibody as a result of illness produced by an unrelated bacterial agent. Walker[4] found no significant rise in typhoid agglutinins in a study of successive serum specimens of patients inoculated with typhoid vaccine suffering from nonenteric febrile illness. Similarly, Perry[2] reported no elevation in the titer of typhoid antibodies in 5 typhoid-immunized patients in whom serial determinations of antibodies were made during the course of nonenteric febrile illnesses.

It was the purpose of this investigation to determine whether a nonspecific increase in some of the antibodies found in the serum of young persons as a result of previous immunization or infections occurs in the course of a variety of febrile illnesses. Because all of the persons studied had recently received typhoid vaccine, typhoid H and O antibodies were chosen for study, as the serum of such individuals usually possesses measurable quantities of these antibodies. Serial antibody titers for viruses of influenza A, A′, and B, and mumps were also studied, since many of these persons would show measurable antibody at the time of onset of illness to these agents as a result of previous infection.

Specimens of serum in the acute and convalescent phases were obtained from 32 young adult febrile patients

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who had previously been immunized with typhoid vaccine and examined for typhoid, influenza and mumps antibodies.

Materials and Methods. SUBJECTS. The persons studied were medical students and student nurses, 24 women and 8 men. The age range was 18 to 33 years. Except for one person (Case 27), in whom a diagnosis of typhoid fever was made 10 years previously, and another (Case 31), who was immunized 8 years previously while in the Armed Services, all were immunized in this institution with New York State Department of Health typhoid vaccine (1000 million bacilli per cc.) using an inoculum of 0.5, 1.0 and 1.0 cc., subcutaneously at weekly intervals.

ANTIGENS. The antigens employed were, (1) bacterial antigens of *Salmonella typhosa* (New York State Department of Health) used for H and O agglutination tests, and (2) influenza A-PR8, A′-FM-1, B-Lee, and mumps (viral type) virus complement-fixation antigens.† The antigens were diluted in 0.85% saline solution.

SERUMS. Specimens (acute phase) were obtained from patients with febrile illness at the time of admission to the hospital. A second specimen (convalescent phase) was obtained 14 days later. Appropriate immune serums were used as controls in the complement-fixation tests.

CONTROL SERIES. A control series which consisted of students who were inoculated with typhoid vaccine but who had no febrile illness was likewise studied. Serial serum specimens obtained at an interval of 2 weeks were examined for changes in serum antibody levels to the antigens mentioned above.

AGGLUTINATION TESTS. Serial twofold dilutions of serum were prepared in saline in 0.5 cc. volumes. One-half cubic centimeter of the appropriate antigen was then added. After incubation at 52° C. for 2 hours, the tubes were stored in the refrigerator (5° C.) overnight. Readings were made after approximately 18 hours in the refrigerator. Titers are expressed in terms of the initial dilution of serum.

COMPLEMENT-FIXATION TESTS. The Kolmer-Boerner complement-fixation technique using overnight refrigeration was employed. Twofold dilutions of inactivated serum (56° C. for 30 minutes) were prepared in saline in 0.25 cc. volumes. Two units of antigen (0.25 cc.) and 2 units of complement (0.50 cc.) were added to each twofold dilution of serum. Following overnight refrigeration at 6 to 8° C., 0.50 cc. of sensitized sheep cells was added. Readings were made after 15 minutes' incubation at 37° C. Complete fixation of complement was used as the endpoint. The titers are given in terms of the initial serum dilutions.

Results. This investigation was made during an influenza A′ epidemic. A unique opportunity, therefore, to study changes in specific antibody, as well as possible changes in unrelated serum antibodies, presented itself. In the evaluation of antibody changes, only those changes which were fourfold or greater were considered significant.

Table 1 presents the data in 14 cases in which the diagnosis of A′ influenza was made on serologic grounds. Furthermore, a strain of A′ influenza virus was isolated from Case 17. Attempts to isolate influenza virus were not made in the remaining cases in the series. A significant change in antibody level to the typhoid O and H antigen was not demonstrated in any case. The relatively high titer of typhoid O antibody in contrast with the H titer in Case 11 is unexplained. No member of this series showed a measurable amount of antibody for influenza B, and only one, Case 16, showed antibody present (a titer of 1 to 4 in both serum specimens) for mumps virus. A significant increase in A and A′ influenza antibody was seen in each case.

Table 2 presents serologic data obtained from 18 patients suffering a variety of febrile illnesses. A significant change in antibody level to typhoid H and O antigens was not demonstrated in any case. Likewise, no significant change in the antibody titer to influenza A, and A′ and mumps viruses was demonstrated. Cases 5, 6 and 28 showed an antibody level of 1 to 4 in both serum specimens to the influenza B virus complement-fixing antigen.

†Obtained through the courtesy of the Lederle Laboratories, Pearl River, New York.

The results in both of these series of subjects are comparable with those obtained in the control series made up of persons not suffering a febrile illness who showed no significant changes in antibody titer over a 2-week period.

Discussion. In view of the frequency with which serologic procedures are employed in an effort to establish a definitive diagnosis, a knowledge of the specificity of such reactions is obviously important to a correct interpretation of their significance. If febrile conditions, generally, produce nonspecific elevations of antibody levels, the interpretation of serologic data becomes difficult, if not impossible. Despite the frequently quoted observations that a form of anamnestic reaction occurs with typhoid agglutinins and other antibodies as a result of nonspecific stimuli, such data do not seem to have been well documented in the human host by studies of serial specimens of serum. The study was planned to clarify this issue. Typhoid H and O antibody levels resulting from previous immunization were measured in specimens of serum in the acute and convalescent phases of a variety of febrile illnesses as a means of evaluating changes in the patient's antibacterial antibody response to the stimulus of fever occurring as a result of a variety of nonenteric diseases. A similar study was made of serum antibodies to the viruses of influenza A, A′, and B, and mumps, since many patients show measurable antibody to these agents as a result of previous infection.

Our findings do not substantiate the belief that such nonspecific anamnestic reactions commonly occur even in the presence of readily detected levels of antibody. In no case was a significant increase, that is, fourfold in typhoid H and O antibody titer demonstrated in previously immunized patients, whatever the cause of fever, and, in only a few cases, was any change whatsoever observed. Those persons exhibiting a demonstrable antibody level to mumps virus showed no significant change in titer. A significant change in influenza A and A′ antibody titer was seen only in patients actually ill with influenza

TABLE 1.—TITERS OF ANTIBODIES FOR INFLUENZA AND TYPHOID IN SERUM OF PATIENTS WITH INFLUENZA A[1]

Case Number	Time in Months Since Inoculation	* Days of Fever	Highest Temperature Recorded (C)	Day of Illness Initial Specimen Obtained	Influenza†				Typhoid‡			
					PR8		FM-1		"H"		"O"	
					A	C	A	C	A	C	A	C
4	15	6	39.5	3	–	32	—	32	64	64	16	16
7	13	5	39.6	2	–	8	—	8	32	32	8	8
8	28	4	39.5	1	–	32	—	32	16	32	16	16
9	4	3	38.0	2	–	16	—	16	32	32	32	32
10	16	6	39.8	1	–	16	—	16	64	64	32	32
11	4	5	39.5	4	8	16	4	16	64	64	256	256
12	4	3	38.2	1	–	16	—	16	64	64	32	32
13	3	1	38.0	1	–	32	—	32	256	256	32	32
16	4	4	39.0	5	–	16	—	16	64	64	32	32
17**	24	3	39.5	2	–	4	—	4	64	64	8	8
20	4	2	39.5	1	4	8	—	8	128	256	256	256
25	4	3	39.6	3	–	16	—	16	64	64	32	32
30	3	2	38.8	1	–	16	N.D.	16	128	128	256	256
32	16	3	39.2	2	–	8	—	8	32	32	16	16

* Temperature recorded as 38.0 C. or above
† Reciprocal of highest serum dilution producing 100% complement fixation
‡ Recirocal of highest serum dilution producing easily visible agglutination
A Serum from patient in acute phase of illness
C Serum from patient in convalescent phase of illness
— Indicates titer of less than 1:4
N.D. Test not done
** Strain of A[1] influenza virus isolated from patient

TABLE 2.—TITER OF ANTIBODIES FOR INFLUENZA, MUMPS AND TYPHOID IN SERUM OF FEBRILE PATIENTS

Case No.	Time in Mos. Since Inoculation	* Days of Fever	Highest Temperature Recorded (C)	Day of Illness Init. Specimen Obtained	Influenza†				Mumps		Typhoid‡				Diagnosis
					PR8		FM-1				"H"		"O"		
					A	C	A	C	A	C	A	C	A	C	
1	14	1	38.4	1	4	4	4	4	8	8	8	8	4	4	Pleurisy
2	4	1	38.4	3	–	–	–	–	16	16	32	32	32	32	U.R.I.
3	4	2	38.0	1	8	8	–	4	—	—	32	32	32	32	U.R.I.
5	20	8	39.3	1	8	8	4	4	—	—	256	256	32	32	Atypical pneumonia
6	15	1	39.7	6	8	8	N.D.	N.D.	16	16	32	32	32	32	U.R.I.
14	8	1	38.9	1	8	8	8	8	4	4	128	128	32	16	Bronchopneumonia
15	39	7	38.6	6	–	–	–	–	4	4	256	256	64	64	Inf. Mononucleosis
18	14	12	40.0	2	–	–	–	–	16	8	16	16	16	16	Bronchopneumonia
19	2	3	38.5	2	–	–	–	–	—	—	64	64	64	64	Pharyngitis
21	3	1	39.0	1	8	8	4	4	—	—	256	256	64	64	Gastroenteritis
22	24	6	40.2	1	8	8	N.D.	–	—	—	128	128	16	16	Inf. Mononucleosis
23	99	4	39.2	3	4	4	–	–	—	—	32	32	64	64	Pharyngitis
24	99	3	39.2	2	8	8	4	4	—	—	32	32	16	16	Atypical Pneumonia
26	2	1	38.4	2	8	8	4	–	4	—	256	128	128	128	Pharyngitis
27	120	5	39.1	4	–	–	–	–	—	—	32	32	8	8	Bronchopneumonia
28	4	2	38.0	5	8	8	4	4	—	—	64	64	16	16	U.R.I.
29	4	2	38.2	1	4	4	–	–	32	32	64	64	32	32	U.R.I.
31	96	14	38.5	13	8	8	8	8	8	8	32	32	16	16	P.U.O.

* Temperature recorded as 38.0 C. or above
† Reciprocal of highest serum dilution producing 100% complement fixation
‡ Reciprocal of highest serum dilution producing easily visible agglutination
A Serum acute phase
C Serum convalescent phase
— Indicates titer of less than 1:4
N.D. Test not done
U.R.I. Upper respiratory infection
P.U.O. Pyrexia of unknown origin

A′ (Table 1). The diagnosis of A′ influenza in this series of cases is established on the basis of a significant increase in antibody titer to influenza PR8 and FM-1 strains and a typical clinical course in each case, and is further supported by the presence of a community-wide outbreak of this disease, and the isolation of a strain of influenza A′ virus from 1 case in this series.

Many of the persons incorporated into Table 2 show measurable antibody to the PR8 and FM-1 strains of influenza virus in the acute phase serum specimen, most likely due, in this situation, to recent infection with the etiologic agent in the outbreak referred to above.

Summary. In the cases presented, persons inoculated with a bacterial vaccine (typhoid vaccine) showed no significant increase in the level of circulating antibody (typhoid H and O antibody) in the course of a variety of nonenteric febrile illnesses.

Persons possessing at the onset of unrelated febrile illness measurable serum antibody levels to certain viruses, influenza A, A′, and B, and mumps, showed no change in such serum antibody levels in the course of the unrelated fever-producing illness.

A significant increase in circulating antibody titer to the antigens employed was demonstrated only in those febrile patients in whom the causative agent of the illness, influenza A′ virus, was identical with or very closely related to certain of the antigens used in this study, namely, antigens of influenza A′ and A viruses.

Fever, as a nonspecific stimulus, does not produce an elevation in circulating antibody level to certain bacterial and virus antigens in the human host, and the antibody response is specific for homologous or very closely related antigens.

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SALMONELLA CHOLERAE SUIS.

A CLINICAL AND EPIDEMIOLOGICAL EVALUATION OF 329 INFECTIONS IDENTIFIED BETWEEN 1940 AND 1954 IN THE NEW YORK SALMONELLA CENTER

By Ivan Saphra, M.D.
BACTERIOLOGIST

AND

Michael Wassermann, M.D.
ASSOCIATE BACTERIOLOGIST

(From the Division of Laboratories, the New York Salmonella Center and the Joseph and Helen Yeamans Levy Foundation, Beth Israel Hospital, New York, New York)

The prototype of the Salmonella group, S. *cholerae suis*, was first reported in 1885 as the hog cholera bacillus by Salmon and Smith[9]. One year earlier, the typhoid bacillus, now included in the Salmonella group as S. *typhi*, had been established by Gaffky in Germany. *Salmonella cholerae suis* appeared and still appears occasionally today under various names in the literature; the synonyms *B. cholerae suis*, *B. suipestifer*, S. *suipestifer* (European type or Kunzendorf) and S. *suipestifer* (American type) are most frequently encountered. The first report of a human infection by S. *cholerae suis* was published in this country by Longcope in The American Journal of the Medical Sciences in 1902[7].

There are three Salmonellae which are serologically closely related: S. *paratyphi C* (often referred to as *B. hirschfeldii*), S. *typhi suis*, and S. *cholerae suis* with the subgroups American and European (Kunzendorf) type. All three types have the identical antigenic pattern VI.VII, c-1.5 in the Kauffmann-White Scheme. On fresh isolation, however, the European type generally displays exclusively the second (1.5) H phase and demonstrates the first (c) H phase only on provocation by the Gard technique. *Salmonella paratyphi C* has in addition almost always the Vi antigen which is closely related to that of S. *typhi*, *B. ballerup*, and *E. coli* I. The most important biochemical features which differentiate the three types are shown in Table 1, (Kauffmann[6]). *Salmonella cholerae suis* and S. *paratyphi C* are of world-wide distribution. The epidemiology of paratyphi C fever was reported by Bader in 1953 in a detailed monograph[1] with an extensive bibliography. Pertinent epidemiological data are also found in the paper by Felsenfeld and Young[5]. A recent paper by Zimmerman[14] contains information about S. *cholerae suis* and S. *paratyphi C* isolations in Korea.

In this country and in the adjoining areas, Cuba, Mexico, and Canada, practically only the European type is encountered. Of almost 400 strains received for identification between April, 1939, and April, 1954, at the New York Salmonella Center, only one was a S. *typhi suis* from a human infection. This was obtained from Dr. A. Curbelo, in Havana. Furthermore, 10 strains of S. *paratyphi C* were identified. These 11 strains which caused clinical signs very similar to those produced by S. *cholerae suis* were included in this study. Most

of the isolations came from the United States, particularly from New York (some from our own hospital), New Jersey, Massachusetts and Pennsylvania, but almost all other states were also represented, and furthermore cultures from Cuba, Canada, Mexico, Trinidad, Europe, and Israel were received. In each case a questionnaire was sent out for information about age, sex, source of isolation (feces, blood, and others), clinical history and epidemiological correlation. Approximately 90% returned satisfactory data. After elimination of all cultures of non-human origin and of strains for which adequate clinical and epidemiological information could not be secured, 329 strains received in the 14-year period from January 1, 1940, to January 1, 1954, were available for evaluation.

CLINICAL MANIFESTATIONS. Table 2 shows the clinical manifestations and sources of isolation. The very high number of 144 septicemias without local manifestations, accompanied by a high spiking fever of a few days' and of up to several weeks' duration, is conspicuous. In 19 additional septicemias a more continuous typhoid-like

TABLE 1.—FERMENTATIVE REACTION OF THE MEMBER OF THE S. CHOLERAE SUIS GROUP (Kauffmann[6])

	S. paratyphi C.	*S. cholerae suis American Type*	*S. cholerae suis European Type*	*S. typhi suis*
Arabinose	V	—	—	+
Dulcitol	+	X	X	+ (2–5)
Inosite	—	—	—	—
Trehalose	+	—	—	+
H_2S	+	V	+	—
d-tartrate	+	+	V	—
Citrate	+	+	+	—

Legend: + means fermentation within 1 to 3 days; X means late or irregular; V means variable fermentation; — means no fermentation

TABLE 2.—S. CHOLERAE SUIS CLINICAL MANIFESTATIONS AND SOURCES OF ISOLATION

Clinical Manifestations	*No. of Cases*	*Feces Only*	*Blood*	*Exudate, Sputum, Pus, Spinal Fluid*	*Urine*
Healthy carriers	3	3	—	—	—
Diarrhea (with or without fever) ulcerative colitis	20 3	23	—	—	—
Diarrhea and fever	30	—	30‡	—	—
Fever, septic type	144	—	144	—	—
Fever, typhoidal type	19	—	19	—	—
Bacterial endocarditis	10	—	10†	—	—
Pneumonia, pleurisy					
Upper respiratory infec.	32	—	—	32*	—
Meningitis	7	—	—	7*	—
Septic abortion parametritis	4	—	2	2	—
Cholecystitis, empyema of gallbladder	4	—	—	4	—
Kidney infection, pyelitis	10	—	—	—	10*
Abscesses, focal inflammations	43	—	—	43*	—

See Table 3

* With or without additional positive blood cultures.
† With or without isolation of salmonella from heart valves at necropsy.
‡ With or without additional positive stool cultures.

fever, with enlargement of spleen and occasional rose spots, was reported. These figures are in marked contrast to all other salmonelloses with the exception of typhoid fever. Not one positive stool culture was found in these 163 septicemias. Of 43 localized manifestations, abscesses and other focal inflammatory processes take the first place. There were 11 instances of osteomyelitis and 8 of osteoarthritis.

TABLE 3.—43 ABSCESSES OR OTHER FOCAL MANIFESTATIONS CAUSED BY S. CHOLERAE SUIS WITH ISOLATION OF THE ORGANISM FROM PUS, TISSUE AT OPERATION, SINUSES OR POST MORTEM

Localization	*No.*
Osteomyelitis	11
Osteoarthritis	8
Psoas abscess	6
Prostatic abscess	2
Spleen	2
Breast	1
Brain	1
Peritonitis	1
Subphrenic abscess	1
Liver	1
Leg	1
Cervical adenoma	1
Pharynx	1
Tonsil	1
Otitis media	1
Hip region	1
Buttocks	1
Abdominal wall	1
Acute cellulitis (of hand)	1

Almost all bone structures, as well as joints, were involved, with the shoulder joint most prevalent. As is evident from Table 3, a great variety of other foci was encountered, although in some instances the exact origin of the abscess formation (for instance in psoas abscesses) could not be determined. In all these cases the organisms were isolated from pus. In addition, occasional blood cultures were positive. In 32 instances the clinical features were those of a pneumonia, with positive sputum or blood cultures or both, and those of a pleurisy or empyema, with isolation of *S. cholerae suis* from the exudate and occasionally from blood. There were 10 infections of the kidney and 7 cases of meningitis with isolation of the organisms from urine and spinal fluid respectively. In some of these infections blood cultures were also positive.

In 10 cases of fatal subacute bacterial endocarditis the organisms were isolated from blood during the disease or *post mortem*, or both, or from the heart valves at necropsy. Rarer manifestations were 4 cases of gallbladder empyema and 4 septic abortions. In 2 of these the organisms were recovered from the uterus.

There were only 53 cases of gastroenteritis, 3 of them listed as ulcerative colitis. In 26 of these, including the ulcerative colitis cases, *S. cholerae suis* was only isolated from the feces. Thirty other cases of gastroenteritis, all of them febrile, showed positive blood cultures in addition to the positive stools.

Healthy carriers, one of them a convalescent carrier, were encountered only 3 times. The 2 others had no history of a previous enteritis. The low number of carriers is in agreement with the observation of Edwards, Bruner and Moran[3]. This low figure is so completely out of proportion to that of all other Salmonellae that one may suspect that either something is wrong with our technique of isolating *S. cholerae suis* from feces or that this organism is selectively suppressed in the intestinal tract. (In an *in vitro* experiment, *S. cholerae suis* when cultured together with *E. coli* was almost completely overgrown by *B. coli*, in contrast to *S. anatum*, a type conspicuous by its high carrier rate, which held its own well in the presence of *E. coli*.)

SEX DISTRIBUTION, FATALITY AND CARRIER RATE, SOURCE OF ISOLATION OF S.

CHOLERAE SUIS AS COMPARED WITH 3 OTHER SALMONELLA TYPES. Table 4 gives a comparison of some significant features in which 329 cases of S. *cholerae suis* differ from 300 consecutive infections of SS. *typhi murium*, *oranienburg*, and 100 consecutive infections of S. *anatum*. *Salmonella cholerae suis* has a marked (2:1) preponderance of infected males to infected females, while the 3 other types show an approximately equal distribution of the sexes. The carrier rate of S. *cholerae suis* is less than 1%, while that of SS. *oranienburg*, *typhi murium*, and *anatum* ranges between 9 and 33%. In contrast, the mortality rate of S. *cholerae suis* is 21%; that of S. *oranienburg*, S. *typhi murium*, and S. *anatum* 4.7%, 4%, and 2% respectively. The same difference exists in the high incidence of S. *cholerae suis* isolations from blood and other parenteral sources and the low figure of 26, exclusively from feces. In all other types, positive stool cultures are the rule and parenteral isolations the exception.

TABLE 4.—SEX, CARRIER CONDITION, SOURCE OF ISOLATION OF INFECTIONS OF S. CHOLERAE SUIS IN COMPARISON TO 3 OTHER SALMONELLA TYPES

	No. of Cases	*Male*	*Female*	*Carriers*	*Fatal*	*Isolated from Blood*	*Spinal Fluid Pus, Exudate*	*Stool Only*
S. cholerae suis	329	217	112	3	70	247*	88	26
S. oranienburg	300	152	148	42	14	26	24	250
S. typhi murium	300	165	135	27	12	13	12	275
S. anatum	100	50	50	33	2	0	2	98

* This figure includes 42 instances in which positive cultures were isolated also simultaneously from pus, exudates, spinal fluids, urine, feces.

SEASONAL DISTRIBUTION OF S. CHOLERAE SUIS INFECTIONS AS COMPARED WITH OTHER SALMONELLOSES. When the incidence of large numbers of salmonelloses was followed over a period of 10 years, a definite pattern evolved. From the lowest point of incidence in February there was a continuous increase of cases during the warmer months up to a maximum in October, followed by a decline to the February minimum[12]. *Salmonella cholerae suis* did not follow this scheme. Its peak was reached in March with 46 infections, and the low ebb in October with 17; in the other months the incidence remained fairly constant, with 30 cases. The explanation for this peculiar behavior may be found in the fact, stressed before, that S. *cholerae suis* rarely produces gastroenteritis and carrier conditions. Consequently fecal discharges are not frequent. Moreover, the clinical manifestations, such as septicemias, abscesses, and the like mostly appear weeks or months after the actual infection, in contrast to other salmonelloses which produce clinical signs, particularly diarrhea, within a few hours or days after the infection.

FREQUENCY OF S. CHOLERAE SUIS IN RELATION TO OTHER SALMONELLA TYPES. The incidence of S. *cholerae suis* in our material as compared with the most frequent other types is shown in Table 5. The material was taken from 4000 consecutive human infections from 1939 to 1951. It does not contain cases from military sources and infections with S. *typhi*[11]. These omissions are intentional. Approximately 1000 cases from the armed forces constitute too selective a material. Insertion of S. *typhi* likewise would have obscured the statistics. Most institutions which have sent us their entire material of Salmonella isolations and suspected cultures

for identification excluded S. *typhi* because every laboratory is in a position to establish a typhoid diagnosis with little difficulty. Consequently, only doubtful or mistaken typhoid cultures reached the Center. Their number, about 500, certainly is out of proportion to the actual occurrence. As is evident from this table, S. *cholerae suis*, constituting 7.2% of this selected material, takes the 5th place in frequency after SS. *typhi murium, newport, oranienburg, montevideo*. It surpasses all these types with the exception of S. *typhi murium* by a wide margin in the absolute number of parenteral manifestations, positive blood cultures, and fatalities[10].

TABLE 5.—OCCURRENCE OF S. CHOLERAE SUIS COMPARED WITH OTHER FREQUENT SALMONELLAE TYPES IN 4000 CONSECUTIVE HUMAN INFECTIONS BETWEEN 1939 AND 1941 EXCLUDING S. TYPHI AND CASES FROM MILITARY SOURCES. (THE FIGURES ARE APPROXIMATED.)

Type	*Number*	*Percentage*
S. typhi murium	1460	36.5
S. paratyphi B.	200	5.0
S. cholerae suis	290	7.2
S. paratyphi C.		
S. oranienburg	350	8.8
S. montevideo	300	7.5
S. newport	430	10.8
S. anatum-newington	220	5.5
Other types	750	18.8
	4000	100%

INCIDENCE OF S. CHOLERAE SUIS IN COMPARISON TO OTHER SALMONELLAE AT DIFFERENT AGE GROUPS (Fig. 1). *Salmonella cholerae suis* has a low incidence in children under one year of age. SS. *typhi murium* and *oranienburg* have the highest incidence in this age group and remain comparatively high between the ages of 1 to 5. A remarkable relative increase (almost 100%) occurs in S. *cholerae suis* between the ages of 1 to 5. The incidence drops sharply between the ages of 5 to 20 in all Salmonella types. It increases again between the ages of 20 to 30 in S. *oranienburg*, between 30 to 40 in S. *typhi murium*, and between 40 to 50 in S. *cholerae suis*. All types show a marked increase between 50 to 60, and after that age a uniform drop.

WIDAL REACTION IN S. CHOLERAE SUIS INFECTIONS. The formation of agglutinins is often pronounced, as would be expected in a severe and often protracted generalized infection. The titer against the somatic antigen of S. *cholerae suis* (VI.VII) was found in some instances to be as high as 1:1600 and the serum of a patient with an osteomyelitis had agglutinins against the second H phase (1.5) at a titer of 1:32000. Agglutinins against these antigens therefore may, as in the case of typhoid and paratyphoid infections, serve as an indicator in "fever of unknown origin" and suspected focal processes.

Discussion. *Salmonella cholerae suis* and S. *paratyphi C* occupy a distinct position among the salmonellae. Their high invasiveness and pathogenicity make them a *clinical problem*. The high incidence of septicemias, with or without focal manifestations, and the rarity of gastroenteritis featuring infections with these organisms put them into one category with S. *typhi*, and, to a lesser degree, with SS. *paratyphi A and B*.

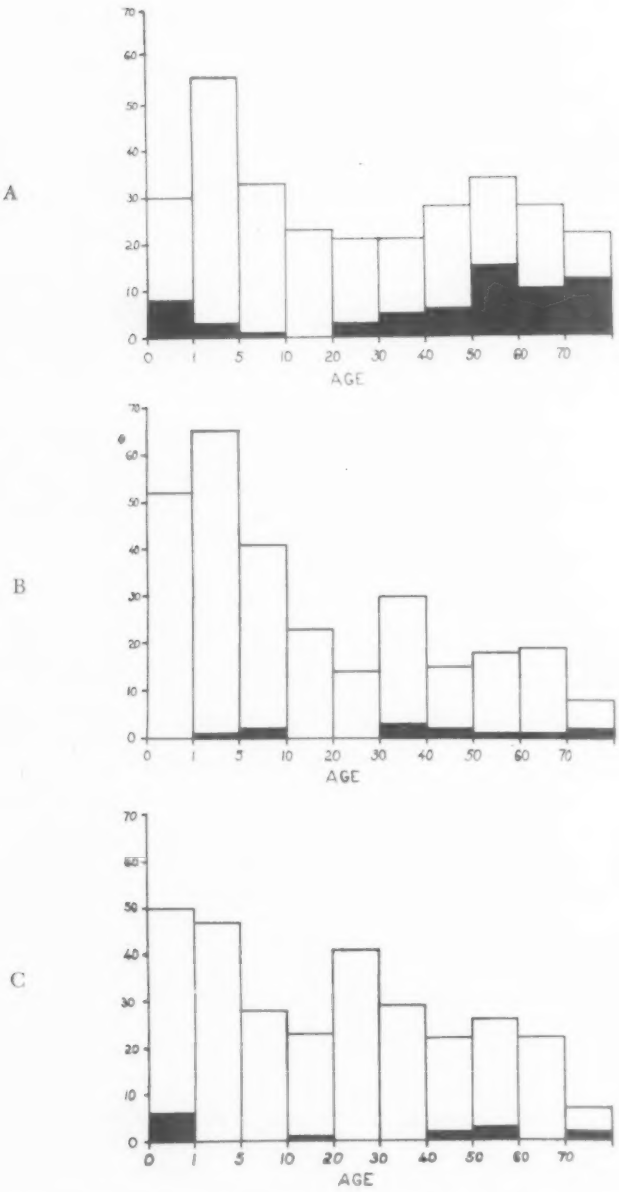

Fig. 1.—Age distribution and fatalities of 295 consecutive infections with *S. cholerae suis* as compared with the same number of consecutive infections with SS. *typhi murium* and *oranienburg*. The empty vertical columns indicate number of cases, the black parts the number of fatalities.

A. *S. cholerae suis* B. *S. typhi murium* C. *S. oranienburg*

They surpass all of the latter in their mortality rate. However, while positive blood cultures are also frequent in typhoid and paratyphoid fever, here as a rule stool cultures become positive at later stages and carriers are frequent. Since the clinical syndrome caused by S. *cholerae suis* is often quite unspecific and may occur in any generalized bacterial or viral infection, the diagnosis of the etiology can only be established by the isolation of the causative organism and can occasionally be hinted at by demonstration of specific agglutinins. The knowledge of the source of S. *cholerae suis*, its way of transmission, and the possibility of its prevention are of definite *epidemiological significance*. As stressed before, the transmission from man to man probably is insignificant because of the rarity of gastroenteritis, the low percentage of fecal excretion, and the negligible number of carriers. Among the entire material of more than 300 infections we found only a single outbreak of 2 consecutive cases within one family, and even in this instance a common outside source could not be excluded. We have, therefore, to look at water, milk, other foods, or animals as the source of S. *cholerae suis* infections. Drinking water, to our knowledge, never has been found contaminated with these organisms. According to Felsenfeld and his coworkers[4], who investigated 1000 milk samples from the Chicago area, not a single S. *cholerae suis* has been found; the same workers cultured salmonellae only 3 times from 500 eggs and from 512 beef specimens isolated only one salmonella. None of these 4 cultures was a S. *cholerae suis*. Among 748 marked fowl, 81 were infected with salmonellae, of which 30% were S. *typhi murium*, 11% S. *oranienburg*, 5% S. *anatum*. Again no S. *cholerae suis* was among the contaminants. Since the second World War, spray-dried egg powder has come into considerable, and well deserved, disrepute because of its very high contamination rate with salmonellae and its role in spreading salmonelloses[8]. As far as S. *cholerae suis* is concerned, however, egg powder should be exonerated. Edwards and Bruner[3] in their huge material of more than 12,000 Salmonella identifications found S. *cholerae suis* only once in egg powder. Soloway, too, and her associates[13] isolated this organism only once from 1969 salmonellae found in egg powder. The corresponding figures for SS. *typhi murium*, *oranienburg*, *anatum*, were 56, 370 and 132 respectively. Of particular interest in this connection are the figures of salmonella outbreaks in general and of S. *cholerae suis* in particular reported in Great Britain[8] from 1923 to 1944. Twenty-two outbreaks were due to S. *cholerae suis*, 665 to S. *typhi murium*, 76 to S. *oranienburg* and 12 to S. *anatum*. In comparison the isolation of Salmonellae from egg powder showed only 4 S. *cholerae suis*, 245 S. *oranienburg* and 30 SS. *typhi murium* and *anatum* each.

Edwards and Bruner[3] demonstrated and confirmed conclusively the observation of Salmon and Smith that the main carrier of S. *cholerae suis* is the hog. Of 1510 outbreaks with 2742 S. isolations among domestic animals as reported by Bruner and Moran[2], 865 outbreaks with 992 positive S. *cholerae suis* cultures came from swine. Only 10 cultures came from cattle, 5 from sheep, 7 from dogs, 33 from other carnivores and 1 from a guinea pig. The corresponding figures for S. *typhi murium* were 329 in 246 outbreaks in all other animals and only 97 in swine. *Salmonella oranienburg* was only found 15 times in 6 outbreaks of animals, 5 in swine; S. *anatum* 58 times in 29 outbreaks in all animals, 33 in swine. It is therefore not surprising

that Felsenfeld[4] isolated from 573 specimens of government inspected pork 83 (14.3%) and from 101 not-inspected pork 27 (26.8%) *S. cholerae suis*. This infestation of pork alone outranked by far that of all other salmonellae combined. Sixty-six per cent of all contamination of pork was due to *S. cholerae suis*, as compared with only 15% by *S. typhi murium*, 2% by *S. anatum* and none by *S. oranienburg*. (In contrast human salmonelloses amount to about 36% infection with *S. typhi murium*, about 7% for *S. cholerae suis*, about 9% with *S. oranienburg*, and 2.5% with *anatum*.)

Felsenfeld also showed that of 102 samples of hamburger hash, 18 (17.6%) were contaminated with salmonellae. Of these, 6 were *S. cholerae suis*, 4 *typhi murium*, and one each SS. *oranienburg* and *anatum*. All these findings point to the hog as a primary reservoir of *S. cholerae suis*. Those factors, so important in the transmission of other salmonellae, appear much less, if at all, instrumental. Although contaminated pork and viscera carelessly handled, raw, or insufficiently cooked, must be considered the main source, the exact mechanism of transmission in an individual case is mostly obscure. There obviously is still much room for epidemiological research. Eating habits explain probably the statistical observation that very young individuals are less apt to acquire a *S. cholerae suis* infection, in contrast to other salmonelloses transmitted by contacts and other food. Also the ratio of 2:1 of men to women is probably due to the fact that more men frequent eating places, cafeterias and often consume their hamburgers "rare," either by intent or default.

Summary. Three hundred and twenty-nine cultures of *S. cholerae suis* (including 10 cultures of the closely related *S. paratyphi C.* and one of *S. typhi suis*), submitted for identification to the New York Salmonella Center between 1940 and 1954 were analyzed for their clinical features and epidemiological correlations. The cultures came from human sources and with adequate information. Most of them were isolated in the 4 Eastern States of New York, New Jersey, Pennsylvania, and Massachusetts. The clinical and epidemiological data are discussed and compared with those of other members of the Salmonella group. The clinical features differ from all other salmonellae, notably SS. *typhi* and *paratyphi A* and *B*, in the rarity of enteric pathology, fecal excretion and carrier conditions, in the frequency of septicemias, and focal manifestations, and in the exceedingly high mortality rate. The very high percentage of isolations from blood and other parenteral sources, pus, exudates, and others, is stressed. *Salmonella cholerae suis* had a conspicuously low incidence in children under one year. Also other differences in age and seasonal distribution compared with other salmonella types were noted. The ratio of infected men to women was 2:1, while in other salmonella types the incidence was approximately equal. The epidemiological evidence points to the hog as a main source of *S. cholerae suis* infections, although the ecological prerequisites of the individual infection are mostly obscure.

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IN VITRO SUSCEPTIBILITY OF MENINGOCOCCI TO ELEVEN ANTIBIOTICS AND SULFADIAZINE*

By Ben Del Love, Jr., M.D.**
ROCKEFELLER FOUNDATION FELLOW; RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL AND THORNDIKE MEMORIAL LABORATORY

AND

Maxwell Finland, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE DIRECTOR, THORNDIKE MEMORIAL LABORATORY, AND CHIEF, FOURTH MEDICAL SERVICE (HARVARD), BOSTON CITY HOSPITAL

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts)

Although meningococcal infections have not increased in incidence during the past 2 or 3 years to the epidemic proportions that had been anticipated[7], they nevertheless constitute a group of important diseases clinically and therapeutically. In the last extensive epidemic, which occurred during World War II, the sulfonamides, especially sulfadiazine, proved highly efficacious both for therapy and for prophylaxis. There was some indication, however, that a slight though definite increase in tolerance of meningococci for sulfadiazine occurred during the course of the epidemic of meningococcal meningitis observed in 1942 and 1943[15]. Most of the antibiotics that have come into wide use since the war are active against meningococci *in vitro*, and some of them have been used successfully in the treatment of meningococcal infections. The present study was undertaken to determine the relative *in vitro* activity of sulfadiazine and of the antibiotics that are currently in general use against strains of meningococci recently isolated from cases of active infection.

Materials† and Methods. A total of 50 strains were available for study. For 39 of these strains we are indebted to Dr. Sara E. Branham, National Microbiological Institute, Bethesda, Md.; the others were from cases observed at the Boston City Hospital and obtained through the cooperation of Miss Marion E. Lamb. Six of the former strains had been isolated between 1948 and 1952; all of the rest were isolated between January, 1953, and April, 1954. Of the 39 strains obtained from Dr. Branham, 29 were from Washington, D. C., 3 from Portugal, 2 from Michigan, 2 from Camp Dix, N. J., and one each from Atlanta, Montreal and Boston; a few of these strains had been preserved in the lyophilized state, the rest on serum-dextrose

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**Now Instructor in Medicine, Meharry Medical College, Nashville, Tennessee.

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agar. The sources of all the strains and their serologic types are summarized in Table 1.

In this laboratory, heart-infusion agar (Difco) to which 10% defibrinated horse blood was added was used for subcultures of the strains and also to incorporate 2-fold dilutions of sodium sulfadiazine and antibiotics in the tests for sensitivity. Each of the strains was grown for 24 hours on a blood agar plate, a 2-mm. loopful was scraped from the surface, thoroughly emulsified into 1 cc. of brain-heart infusion broth (Difco); a loopful of this emulsion (estimated by dilution plate counts to contain about 10^6 viable organisms) was then used to streak a segment of each of the series of sulfadiazine and antibiotic-containing blood-agar plates and on control plates containing no antimicrobial agent. The plates were then incubated at 37° C. and inspected for visible growth with the aid of a hand lens after 24 hours, and again after 48 hours. The sensitivity of a strain was defined as the minimum concentration of the antimicrobial agent in the agar on which no visible growth was discernible after 48 hours. A few of the strains were also tested for sensitivity to penicillin and sulfadiazine using the starch, casein-hydrolysate medium of Mueller and Hinton[14] simultaneously with the corresponding tests on blood agar.

TABLE 1.—TYPES AND SOURCES OF STRAINS OF MENINGOCOCCUS INCLUDED IN THIS STUDY

	Type				
Source	*I*	*II*	*IIα*	*?*	*Total*
Cerebrospinal fluid	0	16	6	5*	27
Blood	1	3	3	7	14
Throat	1	2	2	1	6
?	1	1	1	0	3
All sources	3	22	12	13	50

* One of these was obtained from the brain at necropsy.

Results. The results obtained with all the strains are summarized in Table 2 and are represented graphically in Fig. 1. For comparison there are also included the results of tests for penicillin sensitivity of 54 strains of meningococcus done in this laboratory in 1945 or earlier[11]. On the basis of weight, penicillin was the most active and erythromycin, though considerably less active, ranked next. The least active agents were bacitracin and polymyxin, these being considerably less inhibitory than sulfadiazine and the 7 remaining antibiotics (tetracycline, chlortetracycline, oxytetracycline, chloramphenicol, streptomycin, neomycin and carbomycin), all of which appeared to be fairly comparable quantitatively. The somewhat poorer showing of chlortetracycline as compared with that of its 2 chemical analogues is probably explicable on the basis of its greater lability under the conditions of these tests.

A comparison of the susceptibility of the earlier and the current series of strains indicates a remarkably close similarity. The apparently greater sensitivity of the recent strains is only slight and is probably no more than might be expected from the limits of error of the method and the differences in materials and techniques used. These results certainly give no indication of the appearance of strains of increased resistance to penicillin during the past few years.

The susceptibility of different strains to each of the antibiotics appeared to be fairly uniform, considering the crude method employed. There was a much greater variation, however, with respect to the sensitivity of the strains to sulfadiazine, the minimum inhibiting concentrations ranging from 0.4 to 400 micrograms per cc. These results are much different from those reported by Schoenbach and Phair[15]. Their 430 strains were isolated, in 1942 and 1943, and tested on Mueller-Hinton agar, approximately 100 organisms being spread uniformly over the surface of each sulfadiazine-containing plate. By that method, approximately 10% of the strains were inhibited by less than 0.05 microgram of sulfadiazine per cc.

(<0.005 mg. per 100 cc.), and about 59, 29 and 2% were inhibited, respectively, by 0.05, 0.5 and 5.0 micrograms per cc. The difference in the size of the inoculum may account for some of the difference in these results[6], but the possibility that strains of increased resistance to sulfadiazine have appeared in the interval between these studies seems to be a more likely explanation of the difference observed.

A comparison of blood agar and Mueller-Hinton agar in tests for sensitivity to sulfadiazine and penicillin was also attempted. Tests for sulfadiazine sensitivity of 9 strains were carried out on both media simultaneously on 3 separate occasions. The results are

TABLE 2.—IN VITRO SUSCEPTIBILITY OF STRAINS OF NEISSERIA MENINGITIDIS TO ELEVEN ANTIBIOTICS AND TO SULFADIAZINE

Antibiotics	*Number of Strains*	*Minimum Inhibiting Concentration, Micrograms per cc.**									
		0.004	*0.01*	*0.02*	*0.04*	*0.1*	*0.2*	*0.4*	*0.8*	*1.6*	*3.1*
		Per Cent of Strains									
Penicillin	50	4	34	34	14	10	4				
Penicillin†	54		6	50	17	17	9	2			
Erythromycin	48				2	6	33	23	19	15	2
		0.4	*0.8*	*1.6*	*3.1*	*6.3*	*12.5*	*25*	*50*	*100*	*200*
		Per Cent of Strains									
Chlortetracycline	49			12	51	25	10	2			
Oxytetracycline	49	8	26	37	29						
Tetracycline	49	2	31	47	18	2					
Chloramphenicol	49		16	31	41	12					
Carbomycin	32		6	21	24	28	9	12			
Streptomycin	49			6	31	53	8	2			
Neomycin	32			3	31	44	22				
Bacitracin	49			2	—	2	2	2	16	41	35
Polymyxin B	32							38	38	22	3
Sulfadiazine	50	6	10	20	10	14	12	10	6	—	12‡

* After incubation for 48 hours.
† These strains isolated and tested in 1945 or earlier;[11] all others were isolated and tested between August 1953 and May 1954.
‡ Includes 1 strain (2%) inhibited by 400 μg. per cc.

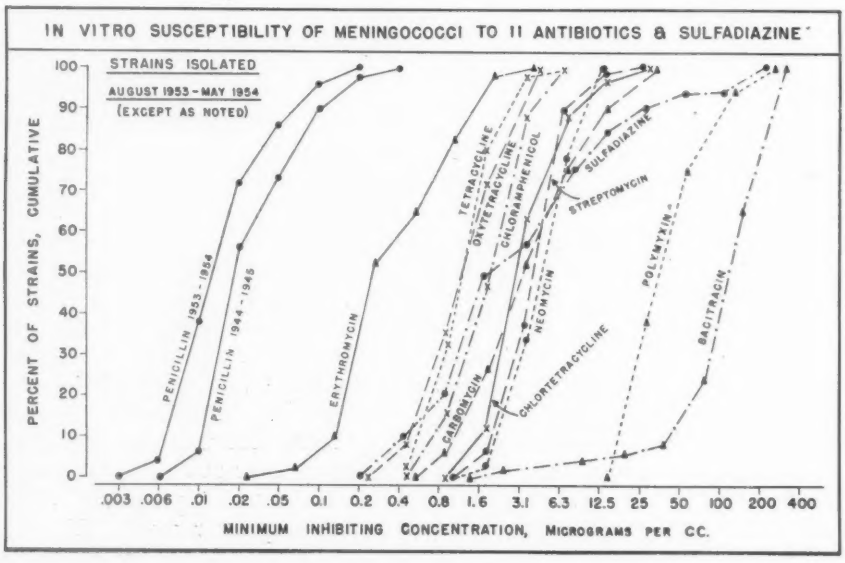

Fig. 1.

shown in Table 3; they show considerable variations in tests done with some of the strains on different occasions, even in the same medium. Some of these differences may have been due to variations in the numbers of organisms inoculated in the different tests. The results obtained with the 2 media on any given day were generally more comparable, but there were appreciable differences, some of the strains appearing to be more susceptible to the sulfadiazine in the Mueller-Hinton medium. Similar tests with penicillin carried out simultaneously in both media yielded more uniform results; in 18 comparative tests the endpoints were identical in both media in 7 and varied by only a single dilution in the remaining 11, the larger concentration being required on the Mueller-Hinton medium in each of these 11 tests.

TABLE 3.—RESULTS OF REPEATED TESTS FOR SENSITIVITY OF MENINGOCOCCI TO SULFADIAZINE DONE EACH TIME SIMULTANEOUSLY ON TWO DIFFERENT CULTURE MEDIA

		Minimum Inhibiting Concentration, Micrograms per cc.			
		10% Horse-Blood Agar		*Mueller-Hinton Agar*	
Strain Number	*Date of Test*	*Partial, 24 hr.*	*Complete, 48 hr.*	*Partial, 24 hr.*	*Complete, 48 hr.*
42	May 29	0.8	3.1	0.8	3.1
	June 8	0.4	1.6	0.4	3.1
	June 11	0.8	6.3	0.2	3.1
43	May 29	12.5	12.5	0.8	3.1
	June 8	0.4	1.6	0.4	3.1
	June 11	3.1	12.5	0.4	3.1
44	May 29	50	200	3.1	12.5
	June 8	6.3	12.5	1.6	12.5
	June 11	12.5	200	12.5	25
45	May 29	12.5	50	1.6	25
	June 8	1.6	25	0.8	12.5
	June 11	6.3	50	1.6	25
46	May 29	1.6	12.5	1.6	6.3
	June 8*	0.4	0.4	0.4	3.1
	June 11	0.4	6.3	0.4	12.5
47	May 29	1.6	3.1	1.6	6.3
	June 8*	0.4	0.4	0.4	3.1
	June 11	0.4	6.3	0.2	12.5
48	May 29	400	400	400	400
	June 8	3.1	50	6.3	12.5
	June 11	25	400	50	400
49	May 29	1.6	12.5	1.6	12.5
	June 8	0.4	1.6	0.4	3.1
	June 11	1.6	3.1	0.8	12.5
50	June 8	0.4	0.8	0.4	0.4
	June 11	0.8	12.5	0.4	6.3

* Scant growth on control blood agar containing no sulfadiazine.

Discussion. The marked change in the susceptibility of pathogenic staphylococci to antibiotics[4], with the appearance and increase in incidence of strains of high resistance to penicillin and then to chlortetracycline and oxytetracycline following the widespread use of the corresponding agents, has necessitated a re-evaluation of the place of the available antibiotics in the treatment of infections with these and many other organisms. Even before this occurred, the sulfonamides, which were so highly effective against gonococcal and hemolytic streptococcal infections when first introduced, had already given way to penicillin for the

treatment of these infections; this was due not only to the greater initial sensitivity of the causative organisms to the antibiotic, but chiefly because of the appearance and rapid spread of sulfonamide-resistant strains of gonococci[1] and hemolytic streptococci[2].

The origin of the increased numbers of resistant strains remains controversial. According to the view most widely held, they result from the elimination of sensitive strains during the presence in the body of any partially effective concentrations of the antimicrobials concerned, thus permitting only the more resistant ones to survive, multiply and spread. In an alternate view, originally sensitive strains increase gradually in resistance during exposure to sublethal concentrations of the agents. Regardless of their origin, however, the observed increases in resistance have accompanied the widespread use of the agents concerned not as treatment for primary infections with the organisms involved, but in the treatment of many other conditions, and particularly for prophylaxis in the absence of overt infections.

Experimentally it has been possible to increase the resistance of meningococci to sulfadiazine[15], penicillin[5,12] and streptomycin[13]. The present study did not reveal any strains of meningococci that were highly resistant to any of the most widely used antibiotics. The present findings, however, suggest that some strains of increased resistance to sulfadiazine are already present and that the degree of this resistance may be sufficient to render ineffective the treatment of infections with such strains. The data are not entirely conclusive in this respect, but the wide range of the minimum inhibiting concentrations of sulfadiazine required by different strains lends further support to this possibility.

Nevertheless, the fact that even under the rigid conditions of the test, which employed a very large inoculum (*Cf.* Ref. 6), all but a small proportion of the strains were completely inhibited by 50 micrograms of sulfadiazine per cc. (5 mg. per 100 cc.) or less, which is well within the concentrations of this agent that can readily be maintained in blood and cerebrospinal fluid, indicates that sulfadiazine may still be the drug of choice for most cases of meningococcal infections. The various antibiotics tested, including pencillin and erythromycin, though they may be more effective *in vitro* on a weight basis against many or all of the strains, have the disadvantage that large amounts are necessary to sustain bactericidal concentrations in the blood, and for most of them such concentrations are not readily achieved and maintained in the cerebrospinal fluid[3,16]. Nevertheless, some of these antibiotics, including penicillin, the tetracyclines and chloramphenicol, have proved effective in the treatment of cases of meningococcal infections, including meningitis[8]. The early results which indicated a distinct superiority of sulfadiazine over penicillin in the treatment of meningococcal meningitis[9,10] were achieved with small doses of penicillin and is not necessarily true when massive doses of the antibiotic are used.

In this study, which included only strains from endemic cases, type I strains were infrequent. There was no correlation, however, between the types of strains and their sensitivity to any of the agents used in this study, and the same was true in the previous study with penicillin[11], in which type I strains were more frequent, and in Schoenbach and Phair's study with sulfadiazine[15] in which type I strains predominated.

Summary and Conclusions. The results of *in vitro* tests for sensitivity of

recently isolated strains of meningococci to 11 antibiotics and to sulfadiazine have been presented. Weight for weight, penicillin was by far the most active agent, and erythromycin ranked next; polymyxin B and bacitracin were the least active. Sulfadiazine and the other antibiotics tested (chlortetracycline, oxytetracycline, tetracycline, chloramphenicol, streptomycin, neomycin and carbomycin) had intermediate and similar activity against most strains. The strains varied only within a narrow range in their sensitivity to each of the antibiotics but their susceptibility to sulfadiazine varied over a wide range. Six of the 50 strains were moderately resistant to sulfadiazine by the test used, and the possibility that this may represent an increasing resistance of meningococci to sulfadiazine is discussed. On the other hand, a comparison of the penicillin-sensitivity of the strains isolated recently and those isolated and tested in 1945 or earlier gives no evidence of increasing resistance of meningococci to pencillin.

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ANOREXIA, IRRITABILITY, AND CONVULSIONS:

EVIDENCES OF SUBDURAL HEMATOMA IN INFANCY

By William R. Chambers, M.D.
ATLANTA, GEORGIA

As Mercer has recently pointed out, "The frequency with which subdural hematomas are found in infancy is directly related to the clinician's awareness of the condition"[8]. The consequences to the child are so serious when adequate treatment is not instituted that it is important that all physicians be aware of this condition. Fincher[2] has suggested it as a cause of microcephalus. Mercer describes the importance as follows: "The seriousness of the subdural hematoma in infancy and the urgent necessity for making a diagnosis and instituting treatment are related to the relatively rapid growth of the brain in the first year of life. The presence of a large membranous subdural hematoma exerts a constricting force on the rapidly growing brain with the production of brain atrophy and mental retardation"[8]. In the metropolitan area in which the author resides, it is estimated that there are more than 5,000 mentally retarded children. If only a small fraction of such cases could be prevented by prompt and adequate therapy and if this were multiplied for all metropolitan areas over the United States, much public expense and discomfort would be avoided. Attention is therefore called to the clinical features and diagnosis of this condition and 5 case reports from the author's experience are presented.

The *incidence* is much greater than is generally thought. Saunders, writing in 1948, on "Intracranial Hemorrhage in the Newborn"[9], quotes McGregor as showing intracranial hemorrhage as a cause of death in 39% of necropsies of 358 infants. He also quotes Geohagan as showing an incidence of 21% in 232 cases. The great majority of the hemorrhages were of the subdural type.

The *diagnosis* is not ordinarily an easy one for the general diagnostician and surgeon or even for the pediatrician. This is partly because the signs are often not prominent, but insidious and misleading, and also because it has become fixed in many minds that convulsions, irritability, and anorexia are expected phenomena in infancy and are often due to inconsequential events. Teething, upper respiratory infections, and gastrointestinal upsets are popularly blamed for such disturbances. Shanks, writing on the nature of infantile convulsions in 1949, makes no mention of subdural hematoma as a possible cause[10]. Lennox, in the same year, discussing febrile convulsions in childhood, states "Half of the children under one year of age had severe convulsions, some of which were followed by transient or permanent neurological sequelae, such as hemiparesis or retarded mental development," and yet he does not consider subdural hematoma as an etiological factor[7].

The *history* is of prime importance and yet may be completely negative. It is helpful, as Saunders[9] points out, if there is a history of precipitate labor, prolonged second stage, breech presentation, internal version and extraction, or difficult forceps. It is also of some aid to know that the mother was a primipara or that the infant weighed 5½ pounds or less at birth. Such history, however, is often lacking. The com-

monest symptom, according to Kinley, Riley, and Beck[6], is some type of gastrointestinal upset. Ingraham and Matson list the symptoms in a large series in their order of frequency as follows: convulsions, vomiting, hyper-irritability, infection, stupor, and history of birth trauma[4]. It must be remembered, however, that any and even all of these events may be absent. Convulsions, for example, were present in only 55.8% of Ingraham's and Matson's cases[4]. It might well be said that any child who is not doing well in spite of adequate and conscientious care should be suspected of subdural hematoma.

The *signs* may be as elusive as the history. Mercer[8] points out that in diagnosing, the most important point to remember is that no abnormality may be encountered on physical examination. There may be periodic exacerbation and remission of signs. Subdural hematomas in infants develop in such a manner that bleeding may occur, the brain become readjusted to the intracranial mass, and then a fresh hemorrhage ensue. A beautiful illustration of this point is the case of Williams[11] who demonstrated, on necropsy, three separate subdural sacs, the oldest one occupying a position closest to the brain. Enlarging head and bulging fontanelle, although of great value when seen, have been over-emphasized as essentials of diagnosis in the past. Ingraham and Matson[4], in their large series of cases, found a bulging fontanelle in only 36% and enlarging head in only 29.2%. Fever, so often thought to be the cause of convulsions, was present in 56.5% of their cases and appears to be directly related to the subdural hematoma, rather than to infection. It is an old axiom that either blood or pus under pressure will account for hyperthermia and leukocytosis. The series of physical findings in order of importance as listed by Ingraham and Matson[4] are: fever, hyperactive reflexes, bulging fontanelle, anemia, enlarged head, abnormal fundi, paralysis, and fracture of the skull. Saunders[9] mentions how difficult the differential diagnosis may be from atelectasis, hypoglycemia, tetany, and congenital heart disease. It must also be remembered that hydrocephalus should not be too readily diagnosed because of the enlarging head. Ingraham[4] pleads that infants suspected of having incurable hydrocephalus should never be abandoned until subdural hematoma is ruled out.

The diagnosis can nevertheless be made with certainty, and by a very simple and safe procedure: a subdural tap through the anterior fontanelle. If proper precautions are taken, no serious consequences are to be expected. The baby's head, except in cases where the hair is unusually thick, is not shaved, since small razor lacerations of the tender skin may give access to infection. It is, however, well-scrubbed to get rid of any possibility of cradle cap and sterile precautions are taken. A number 18 needle with stylet is inserted at least a full thumb's breadth from the midline, but not quite to the far lateral limits of the fontanelle, and is advanced slowly. There is a sharp snap as the needle pierces the dura, and the stylet is withdrawn. More than 1 cc. of fluid of high protein content is considered to represent a subdural hematoma. Subdurals in infants are generally bilateral and taps of both sides should be performed. Naturally, such a tap will not reveal a subdural hematoma that does not underlie the area tapped and, while rare, such subdural collections do exist. If the condition is suspected and no abnormal fluid is obtained in this region, then the needle can be advanced into the ventricle and a ventriculogram through the fontanelle performed with very little difficulty.

Treatment has developed rapidly in

the past 10 years. It was at first considered by those experienced in this field, and it is an opinion still held by many, that if the fluid accumulation can be eliminated by repeated taps, no further treatment is necessary. Recent advances would indicate that such an opinion is in error. Mercer[8], and Jackson and Werner[5] state that treatment should not be limited to the removal of the accumulated fluid which compresses the brain but must be combined with excision of the constricting subdural membranes. Grunagle also states: "Mere washing out is inadequate and has resulted in a high percentage of mental retardation and blindness"[3]. Elvidge and Jackson[1] and Mercer[8] also imply in their articles that operation is imperative. In fact, Mercer[8] says that when the subdural space has been dry during 2 or 3 repeated taps, the patient is ready for surgical exploration. It is the author's opinion that surgical exploration should be adequate as well as prompt. Small trephine openings are no longer considered sufficient exposure for the removal of the membranes in a manner to obtain the best results. After the subdural fusion has been gradually reduced by repeated tapping, comparatively large craniotomies are done a week or 10 days apart, first on one side and then on the other. In this way, the mortality is minimal. In the author's cases, there have been no operative deaths. In a large series reported by Ingraham and Matson[4], deaths have been held to 5.3%. As cases come earlier for treatment, even this low mortality rate can be expected to diminish.

Fig. 1.—Tapping the anterior fontanelle for diagnosis of subdural hematoma.

The following 5 cases are representative of the author's series and illustrative of certain points already discussed.

Case Reports. CASE 1. C. M., aged 5 weeks, was admitted to the hospital because of lethargy, one bout of vomiting, and convulsive twitchings in the left arm which later extended to the left leg. The child was reported to have had no injury or illness of importance connected with birth or from the time of birth to the present illness, except

that, over a period of several weeks, he had begun to shake his head as if he had a headache, to vomit occasionally, and to become very irritable. On examination, the head appeared to be very slightly larger than average. There were no neurological signs present, but the fontanelle appeared to be more tense than normal. Subdural tap revealed a moderate amount of xanthochromic fluid in the subdural space bilaterally. Repeated taps were instituted on a daily basis. The fluid diminished, but did not completely disappear and craniotomy was undertaken, first on the right and later on the left. In each case, a definite subdural membrane was discovered and the brain was found to be displaced by this membrane from 1 to 2 cm. away from the skull. It re-expanded promptly when the membranes were removed. The child recovered rapidly and from then on developed normally without any recurrence of symptoms. At 19 months postoperatively, the development appeared to a pediatrician to be comparable to that of any other normal child of the same age. The patient's general appearance at this time is shown in Fig. 2.

CASE 2. R. B. was brought into the hospital because of anorexia, lethargy, irritability, and diarrhea. There was no history of birth injury. The child had had measles some months before, followed by a febrile period which had been interpreted as pneumonia. Physical examination revealed no neurological abnormalities except that the head appeared large in the lateral diameter, being 18¾ inches in circumference. There was a profound anemia but even when this was corrected, the symptoms did not improve. Bulging of the fontanelle was equivocal. Subdural tap, however, revealed a quantity of xanthochromic fluid, and when this did not clear up on repeated taps, craniotomy was undertaken. The child had an uneventful recovery and continued to improve until, at 11 months postoperatively he appeared to be quite normal in every respect as shown in Fig. 2.

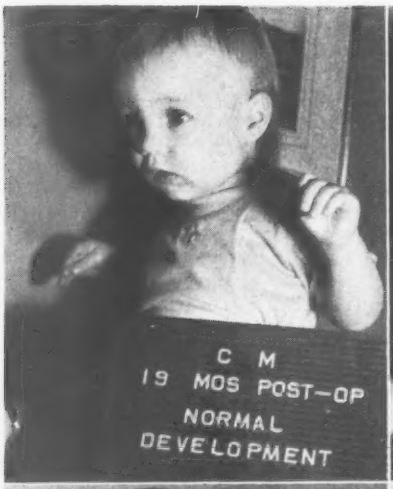
CASE 3. This case is representative of those children who have had an influenzal meningitis and developed an associated subdural effusion. P. P., a 7-month-old colored infant, was admitted to the hospital because of stiff neck and vomiting. She had a high fever with a cough, a marked anemia, a white blood count of 11,700, with 41% lymphocytes. The spinal fluid showed 650 cells, with a protein of 209 mg. and a sugar of 12 mg. per 100 cc. A smear of the spinal fluid showed numerous pleomorphic Gram-negative bacilli and a culture yielded *Hemophilus influenzae*. The child evidently recovered from the meningitis, but continued to do poorly. Subdural taps revealed xanthochromic fluid bilaterally, with a protein content of 2830 mg. When repeated tops failed to improve the infant, craniotomy was undertaken. The child improved very rapidly thereafter and, at one month postoperatively, appeared normal for her age in every respect except for a slight residual enlargement of the head. Her appearance is illustrated in Fig. 2.

CASE 4. P. D., a 4-month-old infant, entered the hospital because of vomiting and sleepiness with irritability. He also had a fever. He was apparently in good health until 4 days before admission when he fell without obvious cause to the floor, striking his head. On admission, the neurological examination appeared to be negative except that the child rubbed his head as if he had a headache. There were hyperactive reflexes in all 4 extremities. The child was vomiting and had a temperature of 100° F. The attending physician, being very thorough and conscientious, had taken head measurements. It was noted from his records that the head had been enlarging rather persistently over the past 2 months. Roentgenograms showed no positive evidence of fracture. The anterior fontanelle was tense, and a fontanelle tap revealed xanthochromic fluid bilaterally. Bilateral craniotomies were done and the membranes removed. At 11 months postoperatively, the child appeared to be normal in every respect as shown in Fig. 2.

CASE 5. R. D. was an 8-month-old infant who was admitted to the hospital in a semiconscious condition. There was no history of convulsion and there was nothing in the parents' story to indicate birth injury. On examination, the eyes deviated to the right. The child could not be aroused except by very painful stimuli and had begun to vomit. The degree of unconsciousness appeared to be deepening. The fontanelle was tense and a subdural tap produced xanthochromic fluid. Taps were instituted and craniotomies were done bilaterally in the usual manner. The child continued to improve. At 10 months postoperatively, he appeared to be normal in every respect as shown in Fig. 2.

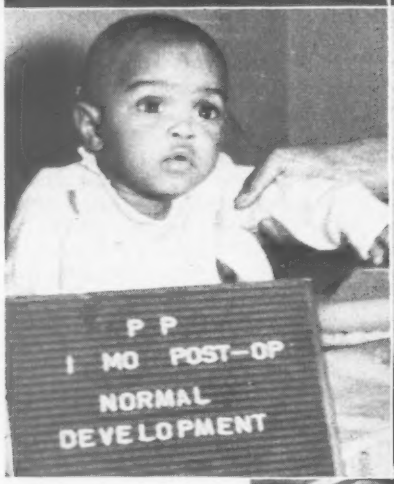
Summary. 1) Subdural hematoma in infants is a condition in which the history and signs may be misleading and confusing. 2) Its incidence is therefore probably higher than is generally suspected. 3) The consequences of inadequate treatment are so serious that all

Case 1

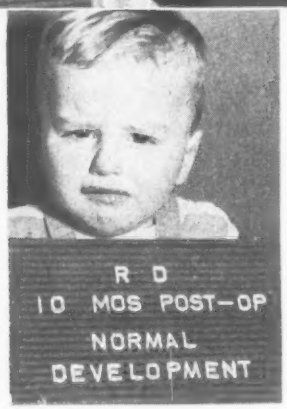


Case 2

Case 3



Case 4



Case 5

Fig. 2.—Case 1: 19 months after operation for subdural hematoma.
Case 2: 11 months after operation for subdural hematoma.
Case 3: One month after operation for subdural hematoma.
Case 4: 11 months after operation for subdural hematoma.
Case 5: 10 months after operation for subdural hematoma.

physicians should be on the lookout for such cases. 4) Thorough treatment by craniotomy with removal of the membranes has been generally satisfactory and the mortality rate has been low. 5) Five representative cases out of the author's experience have been presented.

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OBSERVATIONS ON THE USE OF THE OPIATE ANTAGONISTS NALORPHINE AND LEVALLORPHAN

By James E. Eckenhoff, M.D.
ASSOCIATE PROFESSOR OF ANESTHESIOLOGY IN SURGERY

AND

Lonnie W. Funderburg, M.D.*
ASSISTANT INSTRUCTOR OF ANESTHESIOLOGY IN SURGERY

(From the Department of Anesthesiology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania)

Nalorphine is an effective antidote to poisoning from opiates or opiate-like drugs. The number of agents that can be counteracted by nalorphine remains to be determined. Also, to be elucidated is the optimal dose of nalorphine for use in therapy of depression produced by opiates. Recently, antagonists related to opiates other than morphine have been introduced[1,9]. The relative potency, effectiveness, and interchangeability of these drugs must be explored. The present report attempts to help clarify some of the above factors, as well as to include other observations made with the opiate antagonists.

The report is in four parts: The first demonstrates the effectiveness of nalorphine in counteracting depression produced by Nisentil or by metopon. The second presents data showing that nalorphine and levallorphan appear to be equally effective in counteracting depression produced by either levorphan or morphine. Observations pertaining to effective dosage levels of the antagonists are presented. The third part reports data on the depressant effect of nalorphine used for preanesthetic medication. The fourth part deals with the use of opiate antagonists in obstetrics.

Part 1. The methods used in this part are similar to those reported previously[6]. Large doses of the opiates for study were administered before and during nitrous oxide anesthesia for minor operations not requiring muscular relaxation. Following the surgical procedure, respiratory rate and minute volume were measured by means of a small spirometer. Blood pressure was measured by the auscultatory method. Nalorphine† was injected rapidly intravenously via a previously inserted infusion of 5% glucose in water.

The results of nalorphine counteracting depression produced by Nisentil** and by metopon are summarized in Tables 1 and 2. Respiratory depression was satisfactorily counteracted in all instances. No consistent effect was noted upon the circulation. A variable analeptic effect was observed, being prominent in two, moderate in two, slight in one, and absent in one. Nalorphine (20 mg.) was used in each patient.

Part 2. Similar techniques were employed for this part. Patients were given either levorphan** or morphine with nitrous oxide for anesthesia for the surgical procedure. Following op-

*Present address — 410-A Cotton Avenue, S. W., Birmingham, Alabama.
†Supplied through the courtesy of Merck & Company, Rahway, New Jersey.
**Supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

eration, the depression so induced was counteracted by the use of either nalorphine or levallorphan.* Tables 3 and 4 summarize the data obtained from 7 patients given large doses of levorphan, whose depression was counteracted either by 20 to 30 mg. doses of nalorphine or 5 to 15 mg. doses of levallorphan. Here again an antagonistic effect between levorphan and nalorphine is apparent. It is also obvious that the efficacy of levallorphan is comparable to that obtained with nalorphine. No significance should be attached to relative doses of opiate antagonists used. We were testing the effects of large doses of nalorphine, which accounts for these doses.

TABLE 1.—EFFECTS OF NALORPHINE IN COUNTERACTING DEPRESSION PRODUCED BY NISENTIL IN PATIENTS GIVEN NITROUS OXIDE ANESTHESIA FOR MINOR OPERATIONS

			After Injection				
		Control	*1–2 min.*	*3–4 min.*	*5–6 min.*	*10 min.*	*Analeptic Effect*
E. D., Female							
Age 49 years	Resp. R.	6	17	14	13	Vomiting	
136 lbs.	Min. Vol.	4350	8900	7200	6500		
Nisentil 80 mg.	Pulse	108	108	124	128		+++
Nalorphine 20 mg.	B.P.	120/80	120/80	130/85	130/90		
T. H., Female							
Age 35 years	Resp. R.	9	15	16	17	Vomiting	
166 lbs.	Min. Vol.	3400	9600	9300	8850		
Nisentil 100 mg.	Pulse	90	76	84	—		+
Nalorphine 20 mg.	B.P.	120/75	100/60	105/60	95/55		
M. S., Female							
Age 25 years	Resp. R.	11	20	22	20	20	
128 lbs.	Min. Vol.	4150	10000	9700	7600	6800	0
Nisentil 110 mg.	Pulse	74	76	80	80	76	
Nalorphine 20 mg.	B.P.	90/50	85/50	95/60	100/65	100/65	

TABLE 2.—EFFECTS OF NALORPHINE IN COUNTERACTING DEPRESSION PRODUCED BY METOPON IN PATIENTS GIVEN NITROUS OXIDE ANESTHESIA FOR MINOR OPERATIONS

			After Injection				
		Control	*1–2 min.*	*3–4 min.*	*5–6 min.*	*10 min.*	*Analeptic Effect*
F. B., Female							
Age 51 years	Resp. R.	9	18	20	Awake &		
125 lbs.	Min. Vol.	4100	6900	6850	Alert		+++
Metopon 6.25 mg.	Pulse	72	72	76	72		
Nalorphine 20 mg.	B.P.	120/70	110/60	120/75	125/90		
Y. S., Female							
Age 32 years	Resp. R.	8	18	17	17	20	
133 lbs.	Min. Vol.	4550	8300	7200	6800	8800	++
Metopon 8.5 mg.	Pulse	76	68	84	76	76	Crying
Nalorphine 20 mg.	B.P.	95/70	90/75	90/75	105/70	100/70	
L. T., Female							
Age 23 years	Resp. R.	10	14	16	17		
125 lbs.	Min. Vol.	3550	5600	6400	6800		++
Metopon 6.0 mg.	Pulse	80	84	92	92		Crying
Nalorphine 20 mg.	B.P.	135/85	130/85	140/90	140/90		

Tables 4 and 5 contain data obtained from 8 patients given large doses of morphine. The ensuing depression was counteracted with nalorphine in 4 patients, and with levallorphan in the remaining 4. Observation from the pa-

*Supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

tients included in the morphine-nalorphine series have been included in a previous report[6], but have not been summarized individually. They are reported here for comparison with the morphine-levallorphan data. In the former series, it is noted that relatively small amounts of nalorphine were effective in counteracting respiratory and circulatory depression produced by

TABLE 3.—EFFECTS OF NALORPHINE IN COUNTERACTING DEPRESSION PRODUCED BY LEVORPHAN IN PATIENTS GIVEN NITROUS OXIDE ANESTHESIA FOR MINOR OPERATIONS

			After Injection					
		Control	*1–2 min.*	*3–4 min.*	*5–6 min.*	*10 min.*	*30 min.*	*Analeptic Effect*
M. S., Female								
Age 34 years	Resp. R.	14	22	20	20	18	17	
143 lbs.	Min. Vol.	4650	10550	11000	8800	7550	6450	+
Levorphan 10 mg.	Pulse	72	104	96	92	100	76	
Nalorphine 30 mg.	B.P.	95/55	105/50	115/60	115/60	100/65	100/60	
							20 min.	
M. C., Female								
Age 35 years	Resp. R.	16	21	23	22	19	19	
150 lbs.	Min. Vol.	5000	9250	9200	8350	6450	6850	+
Levorphan 10 mg.	Pulse	92	108	88	104	92	88	
Nalorphine 20 mg.	B.P.	170/70	170/60	170/80	170/80	165/80	160/65	
							40 min.	
L. P., Female								
Age 49 years	Resp. R.	11	18	20	16	16	16	
145 lbs.	Min. Vol.	3750	10100	9600	6700	6400	5440	++
Levorphan 10 mg.	Pulse	112	120	120	128	100	100	
Nalorphine 20 mg.	B.P.	155/85	160/95	165/100	170/105	145/90	130/80	

TABLE 4.—EFFECTS OF LEVALLORPHAN IN COUNTERACTING DEPRESSION PRODUCED BY LEVORPHAN IN PATIENTS GIVEN NITROUS OXIDE ANESTHESIA FOR MINOR OPERATIONS

			After Injection					
		Control	*1–2 min.*	*3–4 min.*	*5–6 min.*	*10 min.*	*20 min.*	*Analeptic Effect*
M. W., Female								
Age 42 years	Resp. R.	9	14	14	15	15	15	
174 lbs.	Min. Vol.	4200	7850	6720	8400	6000	6600	0
Levorphan 10 mg.	Pulse	76	80	88	84	84	84	
Levallorphan 5 mg.	B.P.	130/80	115/70	130/75	135/80	130/80	130/80	
H. S., Female								
Age 30 years	Resp. R.	10	17	19	20	20		+
147 lbs.	Min. Vol.	3800	10200	8000	9600	8800		−
Levorphan 10 mg.	Pulse	82	—	84	88	88		
Levallorphan 10 mg. 5 mg. @ 5 min.	B.P.	120/80	—	140/90	140/95	130/90		
M. C., Female								
29 years	Resp. R.	15	24	29	25	24		+
121 lbs.	Min. Vol.	4750	10550	11600	9000	7700		
Levorphan 15 mg.	Pulse	92	120	124	90	92		
Levallorphan 5 mg.	B.P.	140/70	135/55	150/40	140/50	130/70		
							15 min.	
M. B., Female								
Age 27 years	Resp. R.	12	14	15	15	15	15	
178 lbs.	Min. Vol.	5250	7850	8100	7500	7800	6600	+
Levorphan 12.5 mg.	Pulse	120	110	120	100	120	112	
Levallorphan 10 mg. 5 mg. @ 2 min.	B.P.	150/85	170/100	160/100	160/90	170/90	160/90	

huge doses of morphine. However, these doses had no, or little, analeptic effect against this degree of depression.

Similar antagonistic effects were noted with the morphine-levallorphan group. Small doses of levallorphan appeared to be as effective or more effective than large doses in counteracting morphine depression. The response to the anti-opiates appears to depend up-

TABLE 5.—EFFECTS OF NALORPHINE IN COUNTERACTING DEPRESSION PRODUCED BY MORPHINE IN PATIENTS GIVEN NITROUS OXIDE ANESTHESIA FOR MINOR OPERATIONS

			After Injection					
		Control	*1–2 min.*	*3–4 min.*	*5–6 min.*	*10 min.*	*20 min.*	*Analeptic Effect*
J. H., Female								
Age 24 years	Resp. R.	5	15	—	16	15	13	
157 lbs.	Min. Vol.	3350	6050	—	5800	5100	4700	
Morphine 57 mg.	Pulse	56	60	—	54	54	51	+
Nalorphine 5 mg.	B.P.	70/45	70/45	—	95/60	100/65	105/70	
N. W., Female								
Age 58 years	Resp. R.	3	9	8	8		8	
170 lbs.	Min. Vol.	2000	5400	4050	3600		3550	
Morphine 55 mg.	Pulse	60	54	48	54		60	+
Nalorphine 5 mg.	B.P.	105/75	125/75	135/75	120/75		120/75	
A. G., Female								
Age 28 years	Resp. R.	5	10	13	12	10		
160 lbs.	Min. Vol.	2900	6750	5750	6050	4850		
Morphine 75 mg.	Pulse	80	84	72	76	72		0
Nalorphine 10 mg.	B.P.	125/75	135/85	130/85	120/75	130/80		
E. McK., Female								
Age 29 years	Resp. R.	5	13	14	13	12	12	
167 lbs.	Min. Vol.	3000	8650	8150	6800	5800	5300	0
Morphine 90 mg.	Pulse	92	88	84	84	80	72	
Nalorphine 10 mg.	B.P.	80/60	100/65	100/70	100/70	100/65	100/65	

TABLE 6.—EFFECTS OF LEVALLORPHAN IN COUNTERACTING DEPRESSION PRODUCED BY MORPHINE IN PATIENTS GIVEN NITROUS OXIDE ANESTHESIA FOR MINOR OPERATIONS

			After Injection					
		Control	*1–2 min.*	*3–4 min.*	*5–6 min.*	*10 min.*		*Analeptic Effect*
E. M. B., Female								
Age 39 years	Resp. R.	10	13	17	15	15		
126 lbs.	Min. Vol.	3750	5450	6300	4950	4500		+
Morphine 23 mg.	Pulse	88	84	88	88	84		
Levallorphan 10 mg.	B.P.	110/65	110/70	120/70	95/60	115/70		
							30 min.	
C. A., Female								
Age 23 years	Resp. R.	7	13	13	12	12	13	
111 lbs.	Min. Vol.	2900	4800	4400	4300	4100	4300	
Morphine 30 mg.	Pulse	80	72	64	60	64	68	+
Levallorphan 2.5 mg.	B.P.	115/70	110/70	120/75	115/75	110/70	110/60	
C. H., Female								
Age 24 years	Resp. R.	5	17	18	19	Restless		
190 lbs.	Min. Vol.	1850	6450	6500	6080	&		
Morphine 45 mg.	Pulse	108	114	102	104	Excited		+++
Levallorphan 2.5 mg.	B.P.	110/90	130/90	130/90	140/100			
A. F., Female								
Age 33 years	Resp. R.	5	13	17	16	15		
136 lbs.	Min. Vol.	2900	6750	6100	6400	5400		+
Morphine 35 mg.	Pulse	72	76	70	80	80		
Levallorphan 10 mg.	B.P.	105/70	100/70	120/90	130/90	125/90		

on the degree of depression produced by the opiate. This is demonstrated in Figs. 1 and 2. These figures present the respiratory tracings of 2 patients whose data are summarized in Table 6. It is apparent that 2.5 mg. of levallorphan were more effective in combating depression produced by 45 mg. of morphine than were 10 mg. of levallorphan injected to counteract the effect resulting from 23 mg. of morphine.

PART 3. Because nalorphine has been shown to produce depressant effects similar to those observed following opiates[6,13], we have administered the drug to a small group of patients, scheduled for operation, as a preanesthetic medicament. Twenty-seven patients were given either 10 or 15 mg. of nalorphine subcutaneously and 0.4 mg. of either atropine sulfate or scopolamin hydrobromide, 1 hour prior to the induction of anesthesia. All patients were observed on the ward before the drugs were administered in order to have a base line for judging the effect of the drug. These patients were later observed by the same anesthetist in the operating room. For comparison, 35 patients were given either 5 or 10 mg. of morphine sulfate, 50 to 100 mg. of meperidine, or 1 to 2 cc. of physiological saline, the dose depending upon age, body weight, and physical condition. These latter three solutions were given as unknowns. The results are summarized in Table 7. It is apparent that nalorphine is a potent, depressant drug *per se*.

PART 4. Further observations on the use of nalorphine in parturients and in neonatal infants[7,8] have been made.

We have administered nalorphine in 0.1 to 0.4-mg. dosage to 26 infants via the umbilical cord vein. These infants exhibited depression suggestive of that produced by an overdose of opiates, namely, apnea, cyanosis, and poor muscle tone. The interval between delivery and injection of drug varied from 3 to 22 minutes. Response was considered good to excellent in 23 infants, fair in 2 infants, with no response in one. A good to excellent response was one in which the child began to breathe regularly, color became pink, and muscle tone improved.

TABLE 7.—EFFECT OF NALORPHINE USED FOR PREANESTHETIC MEDICATION

	Dose		*Control*		
Effect	*10 mg.*	*15 mg.*	*Morphine S.*	*Meperidine*	*Saline*
No sedation	5	1*	1	3	12
Good sedation	10	4	5	9	5
Too depressed	4	3	1		
TOTAL	19	8	7	12	17

* Patient wild and hysterical, perhaps the result of excessive dosage.

The intravenous administration of nalorphine to parturients prior to delivery has continued to be an effective method of combating neonatal depression from opiates given the mother. The fear of administration of nalorphine to mothers receiving ether anesthesia[8] has not materialized. We now have no hesitancy in injecting the drug whenever a depression from opiates is encountered, regardless of the anesthetic agent. Further information in this regard will be forthcoming from the obstetrical clinic of this hospital[10].

Discussion. These observations add to the number of drugs proven to be antagonized by nalorphine. So far as the authors are aware, all opiates or

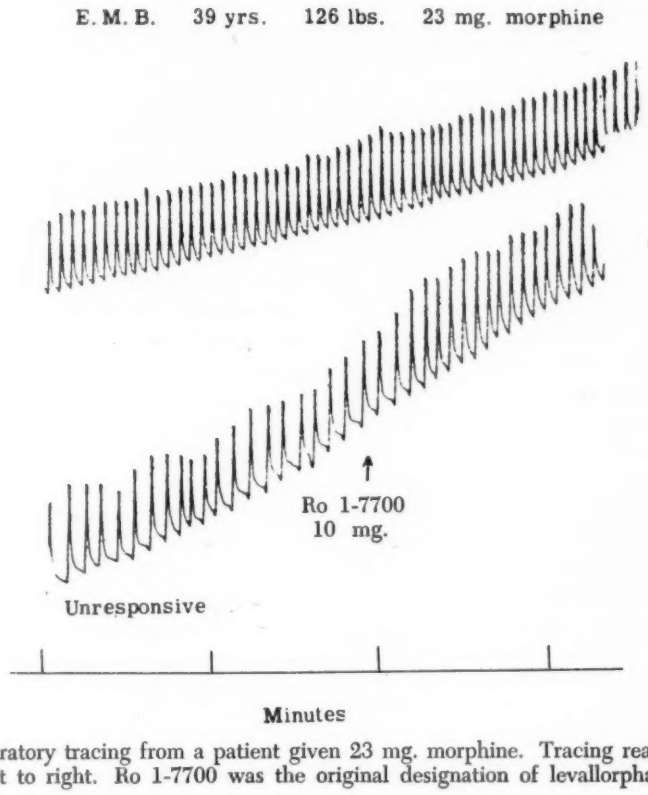

Fig. 1.—Respiratory tracing from a patient given 23 mg. morphine. Tracing reads from lower left to right. Ro 1-7700 was the original designation of levallorphan.

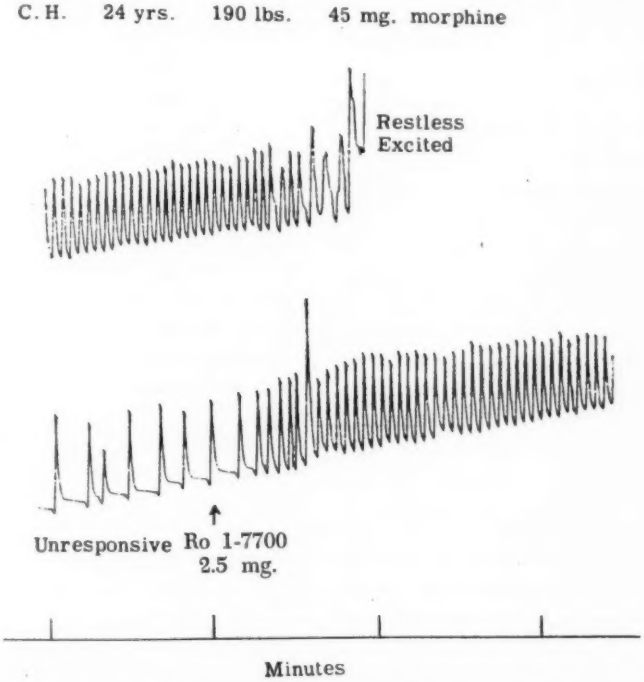

Fig. 2.—Respiratory tracing from a patient given 45 mg. morphine. Tracing reads from lower left to right. Ro 1-7700 was the original designation of levallorphan.

opiate-like drugs tested appear to be antagonized by nalorphine. Such antagonism may occur when nonspecific analeptics such as nikethamide or amphetamine are relatively ineffective[3].

A comparison of the relative effects of nalorphine and levallorphan in counteracting depression produced by morphine or levorphan has been attempted. Both antagonists appear to be equally effective against either depressant. Choice between the two, however, is difficult.

Small doses of antagonists may be effective, despite considerable opiate depression[4,5]. Conversely, relatively large doses of antagonists may have minimal action if the degree of depression is minor. This supports the clinical observation that the opiate antagonists are most effective when the depression for which they are administered is greatest. This may explain the failure of Payne[11] to note a significant response to the drug in outpatients given 15 mg. of morphine. Our observations also support those of Wikler and associates[14] who record that nalorphine administered to patients with minimal depression may facilitate that depression.

Considerable data have been accumulated on the depressant action of the opiate antagonists[2,6,11]. Many of the effects produced by these drugs alone parallel those resulting from opiates such as morphine and meperidine. As noted herein, 10 to 15 mg. of nalorphine produced depression equal to, or greater than, that produced by equivalent doses of morphine. If the patients became ambulatory after nalorphine, the symptoms (that is, nausea, pallor, sweating, and others) were similar to those seen following opiates under similar circumstances. However, the euphoria not infrequently observed soon after administration of morphine was lacking.

Our observations of the effectiveness of nalorphine administered to neonatal infants are similar to those recently reported by Peterson and Prescott[12]. It is technically easier, however, tc inject the drug into one of the mother's veins than it is to inject it into the umbilical cord veins. Our data and clinical observations suggest that the drug can be injected into the parturient whenever neonatal depression from opiates is feared, regardless of anesthetic agents being administered. It is important to realize, nevertheless, that the agent can be given to the infant if the occasion should arise.

Usefulness of the opiate antagonists might be summarized as follows:

1. Their greatest utility appears to lie in the treatment of poisoning from opiates or opiate-like drugs. Of the two antagonists studied by us, there appears to be little choice. Their effectiveness in counteracting minor degrees of depression is not predictable, nor have we always been able to combat unexpected depression resulting from a usual or relatively small dose of opiate.

2. The opiate antagonists are of value in the treatment of parturient or neonatal depression from opiates used to relieve the discomfort of labor. It should not be a routine measure, however. It is technically easier to administer the drug to the mother, although injection can be made directly into the infant. Neither the anesthetic agent nor technique used in the mother appears to be a deterrent to the use of the antagonists.

Considerable attention is being paid to combining opiates and opiate antagonists in order to abolish the respiratory and circulatory depressant effects of opiates yet to preserve the analgesic properties. Such studies are under way in this clinic.

Summary. 1. Data are presented demonstrating that nalorphine is an

effective antagonist to depression produced by Nisentil and by metopon.

2. Levallorphan and nalorphine appear to be equally effective in counteracting depression produced either by morphine or levorphan. Choice between the two antagonists is difficult.

3. The depressant characteristics of nalorphine administered to unnarcotized individuals are emphasized by data from patients who received the drug for preanesthetic medication.

4. Additional evidence is presented to indicate the value of nalorphine in combating neonatal opiate depression. The drug can be given to the mother prophylactically or to the infant therapeutically without regard to the anesthetic agent administered to the mother.

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AMYLOIDOSIS COMPLICATING RHEUMATOID ARTHRITIS

By James M. Reece, M.D.
HEAD PHYSICIAN, INTERNAL MEDICINE, LOS ANGELES COUNTY HOSPITAL; AND INSTRUCTOR IN MEDICINE, COLLEGE OF MEDICAL EVANGELISTS

AND

Telfer B. Reynolds, M.D.
ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA

(From the Departments of Medicine of the College of Medical Evangelists and the University of Southern California, and the Los Angeles County Hospital, Los Angeles, California)

Amyloidosis is generally considered to be a rare complication of rheumatoid arthritis[4], yet Fingerman and Andrus[6] stated that it occurred in 13 of 61 (21%) necropsied cases of rheumatoid arthritis. Three of these had concomitant active tuberculosis. Even so, 10 of 61 cases leaves a high percentage which is encountered in only one other comparable report. Teilum[19] was able to demonstrate amyloid deposits in 20 of 32 cases of rheumatoid arthritis coming to necropsy. Amyloid changes were pronounced in 11 cases. He considered amyloid deposition to be a lesion highly characteristic of rheumatoid arthritis, and presumably one of the most frequent causes of amyloid formation in general. Ropes[13], in discussing a case of rheumatoid arthritis and amyloidosis, stated that in the group at the Massachusetts General Hospital the incidence was less than 10%. He furthermore stated that they had several patients with amyloid disease, and that the usual course was a slowly deteriorating one with gradually increasing renal failure.

Trasoff *et al.*[20], in 1944, reviewed the literature and added a case of their own. They were able to report a total of 32 cases of amyloidosis associated with rheumatoid arthritis. Cases in which arthritic symptoms were probably caused by amyloid deposits in the joints were omitted. Since their paper, an additional 60 cases have been collected from the literature, including 2 reports appearing before Trasoff's article, but not included by them. These collected cases are summarized in Table 1.

Of these 92 total cases, the age of the patient was mentioned in 62. Forty-four of these were over the age of 20.

The simultaneous finding on a single ward of 2 cases of amyloidosis associated with rheumatoid arthritis prompted us to review all the cases of amyloidosis and of rheumatoid arthritis in the Los Angeles County Hospital since 1935. Only 3 additional cases have been found in which these two entities were associated, making a total of 5. The diagnosis of amyloidosis was suggested by the findings of edema, hepatosplenomegaly, albuminuria, and an associated rheumatoid arthritis. The pertinent data will be found in the following case reports.

Case Reports. case 1. A. A., a 67-year-old Caucasian female, was admitted to the hospital in March, 1951, for ankle swelling, anemia, nausea and vomiting, and a mass in the neck which made swallowing and breathing difficult. She had been given four whole-blood transfusions at monthly intervals for the previous 4 months for an unexplained anemia. She had been taking digitalis for 5 months for heart disease of undetermined

etiology. She had received many kinds of treatment including gold, for chronic rheumatoid arthritis of 18 years' duration. The blood pressure was 130/50. Cardiomegaly was present and blowing apical and basal systolic murmurs were heard. A 1-cm. nodule in the mid-portion of the thyroid gland was felt. The liver was palpable 6 cm. below the right costal margin. The kidneys and spleen were not felt. A fusiform swelling of most of the joints of the fingers, with deformities of the feet and elbows, and nodules over the great toes were present. The sedimentation rate was rapid. The hemoglobin was 11.5 gm. per 100 cc., and the leukocyte count was 5,800 with a normal differential. The urine pH was 5.5; specific gravity 1.010; and the albumin test positive (3 plus). The nonprotein nitrogen was 35 mg. per 100 cc. The serum albumin was 2.4 gm., and globulin 2.4 gm. per 100 cc. The icterus index was 7 units, thymol turbidity 3 units, and cephalin flocculation 2 plus. The prothrombin time was 80% of normal. Bromsulphalein retention was less than 10%. The carbon dioxide combining power was 63 volumes %. The protein-bound iodine was 1.5 micrograms per 100 cc. Stool examinations were negative. The electrocardiogram showed only digitalis effect. Roentgenograms of the hands showed typical advanced changes of rheumatoid arthritis. Biopsies of the thyroid nodule, gingivae, and a marrow particle did not show any amyloid. Two Congo red tests at a 3-week interval both showed 100% retention with no appearance of the dye in the urine. She was given 3 cc. of crude liver extract intramuscularly twice weekly for 9 months with questionable benefit, although she stated that she felt better. The serum albumin was 2.7 gm. and the globulin 3.0 gm. per 100 cc. at the start of liver therapy, and after 5 months of treatment the albumin was 3.2 gm. and the globulin 2.5 gm. per 100 cc. A subtotal thyroidectomy was done on February 21, 1952, at which time a 50 gm. multinodular colloid goiter without evidence of amyloid degeneration was removed. Urine concentration study showed an ability to concentrate to a specific gravity of 1.020, but heavy albuminuria persisted. The patient was followed intermittently in the Thyroid Clinic where she received from 0.2 to 0.4 mg. of sodium-levo-thyroxin daily, maintaining normal serum protein-bound iodine and cholesterol levels and a normal basal-metabolic rate. Late in 1952,

TABLE 1.—RHEUMATOID ARTHRITIS AND AMYLOIDOSIS. CASES COLLECTED FROM THE LITERATURE

Author	*Year*	*Less than 20 Years of Age*	*More than 20 Years of Age*	*Age Not Stated*	*Total*
1. Trasoff, *et al.*[20] (Collected cases to date)	1944	11	19	2	32
2. Bach and Savage[2]	1940	2			2
3. Fingerman and Andrus[6]	1943			8	8
4. Young and Schwedel[23]	1944		3		3
5. Rosenberg, *et al.*[17]	1944	1	1		2
6. Massachusetts General Hospital Case No. 31212[13]	1945		1		1
7. Flynn[7]	1945		1		1
8. Coss and Boots[5]	1946	1			1
9. Yeoman and Wilson[22]	1947		1		1
10. Pickard[16]	1947	1			1
11. Unger, *et al.*[21]	1948		10		10
12. Hill[8]	1948		1		1
13. Lush *et al.*[12]	1948		1		1
14. Jennings[10]	1950		2		2
15. James and Bolton[9]	1951	1			1
16. Skelton[18]	1951		3		3
17. Armstrong[1]	1951	1			1
18. Clinicopathological Conference[3]	1952		1		1
19. Teilum[19]	1953			20	20
TOTAL		18	44	30	92
20. Reece and Reynolds	1954		5		5
TOTAL		18	49	30	97

she developed kerato-conjunctivitis sicca (Sjögren's syndrome). Because of this and the continuing severe arthritic symptoms, cortisone was given, generally in 50- to 75-mg. daily doses. This has been continued until the time of writing of this paper. Congo red test, on May 28, 1954, showed 45% retention. On the same date, the serum albumin was 3.6 gm. and globulin 1.9 gm. per 100 cc., thymol turbidity 4 units, and cephalin flocculation negative. No hepatosplenomegaly or edema was present.

CASE 2. A. S., a 44-year-old Caucasian male, was first seen in the Arthritis Clinic in July, 1950. He had migratory joint pains and swelling progressively involving the knees, ankles, wrists, thumbs and shoulders for 2 years, diagnosed and treated as rheumatoid arthritis. For 6 months he had lost weight and strength and had intermittent fever. The knee, ankle, and first metacarpophalangeal joints were swollen, warm, and tender. The fingers were spindle shaped with enlargement of the proximal interphalangeal joints. The sedimentation rate was rapid. He was treated for rheumatoid arthritis with a total of 790 mg. of gold sodiumthiosulfate intramuscularly between July, 1950, and January, 1951, without improvement.

In January, 1951, he began to have increasing diarrhea, consisting of from 4 to 6 loose brown stools daily, and in February, ankle swelling appeared. The urine which had been previously negative for albumin, became strongly positive.

He was admitted to the hospital in March, 1951, at which time the joints were red, swollen, and tender. There was gross pitting edema of both legs. Examination of the heart was negative. The liver and spleen were not palpable. He presented the picture of a nephrotic syndrome with edema, albuminuria (16 to 20 gm. of albumin per 24 hours) and low serum proteins (albumin 1.7 gm. and globulin 2.1 gm. per 100 cc.). The serum cholesterol was 354 mg.; serum protein-bound iodine 1.4 micrograms; nonprotein nitrogen 34 mg. per 100 cc.; and the carbon dioxide combining power 27 mEq./L. There were moderate numbers of granular casts and a few white and red blood cells in the urinary sediment. Blood and urine cultures were negative. Roentgenogram of the chest was essentially negative. Stool examinations and sigmoidoscopy were negative. A barium enema showed only some irritability and lack of haustration in the upper sigmoid region. On two occasions there was 100% absorption of a dose of 12 cc. of intravenously administered Congo red, with no appearance of the dye in the urine. Gingival biopsy was negative for amyloid.

In the subsequent year, his condition gradually deteriorated with the appearance of progressive dyspnea, azotemia, and acidosis. He was last admitted to the hospital on March 2, 1952, at which time he had a terminal bronchopneumonia. The hemoglobin was 9.0 gm. per 100 cc. The leukocyte count was 23,000 with 88% polymorphonuclear leukocytes. Urine pH was 5.5, specific gravity 1.017, albumin test positive (four plus), and the microscopic examination showed many red and white blood cells, and granular casts. The nonprotein nitrogen was 115 mg. per 100 cc., carbon dioxide combining power 7.5 mEq., serum chlorides 109 mEq., and potassium 5.9 mEq. per liter. In spite of the intravenous administration of fluids and electrolytes, the nonprotein nitrogen rose to 129 mg. per 100 cc., and the carbon dioxide combining power fell to 7 mEq./L. The patient died on March 3, 1952.

At necropsy, the heart weighed 440 gm. The left ventricle was dilated and the ventricular wall hypertrophied. There was some beading of the leaflets of the mitral valve. The right lung weighed 1250 gm. and the left 1150 gm. There was marked generalized pulmonary edema. Bronchopneumonia was present in both upper lung lobes. The liver weighed 2530 gm., spleen 410 gm., and kidneys together 300 gm. The adrenals were hypertrophied and weighed 28 gm. each. There was an increase in the synovial fluid, and pannus formation encroaching on the articular surfaces of both knees. Marked amyloid infiltration was seen in the liver, spleen, kidneys, and adrenal glands. No amyloid was found in the heart, tongue, pancreas, sublingual glands, or thyroid.

CASE 3. J. J., a 43-year-old Caucasian female, was first admitted to the hospital in July, 1949. She had suffered from increasingly frequent attacks of red tender swelling of the knee, ankle, and finger joints, associated with fever, for 4 years. Weakness and weight loss had been increasing for 6 months. On examination, the ankles, knees, wrists and proximal interphalangeal joints were red, warm, swollen and tender. The hemoglobin was 9.5 gm. per 100 cc., and the sedimentation rate was rapid. The urine albumin test was negative. Cultures of the blood, urine and joint fluid were negative. A diagnosis of rheumatoid arthritis was made. She remained in the hospital for 6 weeks during which time there was moderate improvement with subsidence of the daily temperature elevations. She returned to the hospital 7 months later with

progression of her joint symptoms, further weight loss, weakness, and continued fever. Ankle swelling had been noticed for 2 months. The joints were warm, swollen, and tender. Pitting edema was present below the knees. The liver and spleen were not palpable. The hemoglobin was 8.0 gm. per 100 cc. The urine contained large amounts of albumin (from 25 to 50 gm. per 24 hours) and a few white blood cells were seen in the sediment. Serum albumin was 1.3 gm. and globulin 2.7 gm. per 100 cc. The nonprotein nitrogen was 28 mg. per 100 cc. Roentgenogram of the chest and retrograde pyelograms were negative. On two occasions there was 100% absorption of intravenously administered Congo red. She left the hospital unimproved and failed to return for follow-up.

CASE 4. W. G., a 23-year-old Caucasian male was admitted to the hospital in December, 1941, because of increasing swelling of the legs of 2 months' duration. He had had a progressively crippling arthritis since the age of 8 years, first involving the knees and later spreading to the hands, ankles, shoulders and back. Swelling and redness in the joints, pain and fever were prominent symptoms until the age of 16; after that they had only been rarely present. He had been confined to bed or a wheelchair since the age of 18. Two months before entry his ankles, and then his legs and abdomen had become swollen. He had noted increasing weakness and occasional nausea and vomiting. He had not had gold therapy. Physical examination disclosed immobility of the spine, fixation of both knee joints in partial flexion, decreased mobility of the ankles and wrists, with flexor and ulnar deviation of the fingers. There was gross pitting, dependent edema and ascites. The blood pressure was 168/110. The urine showed a positive test for albumin (4 plus) on every examination, but the sediment contained only an occasional white blood cell. Phenolsulfonphthalein excretion was practically zero in one hour. The hemoglobin was 6 gm. per 100 cc. The nonprotein nitrogen was 74 mg. per 100 cc. A Congo red test was not done. The patient failed to improve with mercurial diuretics and intravenous acacia. He died one month after entry. At necropsy, the liver weighed 1520 gm., spleen 300 gm., and kidneys together 220 gm. Amyloid deposits were found in the liver, spleen, and kidneys. Nearly all of the glomeruli in both kidneys were replaced by hyalin amyloid deposits. No cause for amyloidosis was found other than the rheumatoid arthritis.

CASE 5. A. F., a 36-year-old Caucasian female, gave a history of recurring arthritis of the hands, wrists, elbows and knees since the age of 21. Swelling and tenderness in the joints was evident during the attacks and there was progressive limitation of motion, particularly in the fingers. Increasing weakness, weight loss and fever began 4 months prior to her entry to the hospital in December, 1938. She was thin, febrile and quite weak. The knees and wrists were moderately warm, red, swollen and tender. There was limitation of motion of the fingers with flexor and ulnar deviation. The liver was palpable 2 inches below the costal margin. There was moderately pitting edema of the ankles. The hemoglobin was 7.0 gm. per 100 cc. The urine test for albumin was positive (4 plus), but the urinary sediment examination was negative. The serum albumin was 2.3 gm. and globulin 2.3 gm. per 100 cc. Serum nonprotein nitrogen was 124 mg. per 100 cc. A Congo red test was not done. She became progressively weaker and died 2 weeks after entry. At necropsy, the liver weighed 1520 gm., spleen 240 gm., and kidneys together 390 gm. Moderate amounts of amyloid were present in the liver and spleen. There was extensive renal glomerular replacement with amyloid. There was bronchopneumonia in the left lung.

Discussion. Amyloid is a glycoprotein in which a mucopolysaccharide (chondroitin-sulfuric acid or mucoitin monosulfuric acid) has been attached to a globulin. Amyloid has a matrix of protein which becomes complex by combination with various other substances of the body fluids, thus accounting for its variable composition from case to case and in different areas in the same case. Amyloid is thus related to the muco-polysaccharides of the amorphous ground-substance of normal connective tissue, which shows involvement in various "collagen diseases," such as acute rheumatic fever, scleroderma, periarteritis nodosa, as well as rheumatoid arthritis.

The exact cause of amyloidosis is as yet unknown. Much experimental work has been done however. Latvalahti[11] concludes that the amyloid-producing agent is some stimulus which places an added strain on the antibody-forming system (particularly the reticuloendo-

thelial system, including the plasma cells). Under this added strain, the immunization mechanism gradually becomes exhausted and the antibody level in the blood becomes inadequate. There is then an excess of antigen in the circulating blood, and an antigen-antibody reaction, that is, the precipitation of amyloid, occurs at the site of origin of antibody formation. This explains why the spleen and liver are so frequently the sites of involvement in secondary amyloidosis.

Teilum[19] stated that amyloid is due to a perverted phase in the cellular synthesis of protein, and that the amyloidosis in rheumatoid arthritis can be explained by an imbalance in the reciprocal effects of ascorbic acid and a hormone of the adrenal cortex of the cortisone type. His view was that an active phase of ribonucleic acid synthesis (pyroninophilia) in mesenchymal tissue cells, accompanied by an accumulation of plasma cells in the reticuloendothelial system, and elevated serum gamma globulin values, was maintained or stimulated by ascorbic acid and inhibited by cortisone. Following the active phase, was one of healing or hyaline change (hyalinosis). Experimentally, the continued administration of cortisone at this stage (with increased ascorbic acid deficit) resulted in a perverted protein synthesis with the formation of amyloid. There is no basic conflict between the theories of Teilum and Latvalahti. Both have shown that in experimental animals cortisone and ACTH promoted the development of amyloidosis. Latvalahti[11] stated that ACTH and cortisone, which suppress antibody formation and reduce the amount of antibodies in the blood, may at the same time as there is an excess of antigen in the blood, accelerate the antigen-antibody reaction and the precipitation of amyloid at the site of antibody formation.

Paulsen[15] reported that, following ACTH therapy in 2 patients with amyloidosis, there was an aggravation of the condition and increased albuminuria. This is at variance with the findings of McCall and Fisher[14] who reported 2 cases of primary amyloidosis of the larynx treated with cortisone, one of which was improved, the other unchanged. A third patient was treated with ACTH and showed considerable improvement.

To date there appears to be no constant association of the appearance of amyloid in rheumatoid arthritis with any form of treatment. Gold therapy, vaccine therapy, and salicylates have all been implicated, but it becomes obvious from review of our cases and those in the literature that these forms of treatment were not always used in each case that developed amyloidosis.

Gingival biopsies in the 2 patients followed on the wards were negative for amyloid. It would seem that needle biopsy of the liver would be of greater value in the diagnosis of amyloidosis, since the liver is so frequently involved. To date, the diagnosis of amyloidosis depends primarily upon a high index of suspicion when seeing a patient with chronic rheumatoid arthritis who also has hepatosplenomegaly, edema, and albuminuria. Congo red absorption of a marked degree confirms the diagnosis, although at necropsy some cases have been reported in which the Congo red absorption was minimal[20].

We are sure that the incidence of cases at this hospital is much greater than we are able to report, since many of the cases of rheumatoid arthritis did not come to necropsy, and many that should have had Congo red determinations did not have them done.

Summary. The case histories of 5 patients with amyloidosis secondary to chronic rheumatoid arthritis are pre-

sented. One patient is still living 4 years after the diagnosis of amyloidosis was made. There is some evidence of regression of the amyloidosis in this case. Whether this is spontaneous, or due to crude liver or cortisone therapy, cannot be determined.

To date, a total of 97 cases of amyloidosis associated with rheumatoid arthritis have been reported.

The association of amyloidosis and rheumatoid arthritis is probably more common than generally recognized.

No specific form of treatment has yet been found to be universally successful in treating amyloidosis.

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THE USE OF RESERPINE IN THE HYPERTENSIVE ARTERIOSCLEROTIC SYNDROME*

By Jack Kleh, M.D.
MEDICAL DIRECTOR, D. C. VILLAGE,
AND CLINICAL INSTRUCTOR IN MEDICINE, GEORGE WASHINGTON UNIVERSITY

AND

Joseph F. Fazekas, M.D.
CHIEF OF STAFF, DISTRICT OF COLUMBIA GENERAL HOSPITAL
AND ADJUNCT PROFESSOR OF CLINICAL MEDICINE, GEORGE WASHINGTON
AND GEORGETOWN UNIVERSITIES

(From the District of Columbia General Hospital and the D. C. Village, Washington, D. C.)

Reserpine† has been reported as a safe and effective agent in the treatment of elderly patients with hypertension[1]. It was found to exert a definite mild hypotensive effect and, in addition, to diminish subjective complaints frequently encountered in such subjects and attributed to their cerebral vascular insufficiency.

In view of these observations, it seemed worthwhile to study the effects of this drug on the cerebral hemodynamics and metabolism of patients with hypertension and cerebral vascular insufficiency.

Material and Methods. Twelve patients were initially included in this study, but complete data were obtainable in only 8 cases. These included 6 men and 2 women, ranging in age from 45 to 72 years, with sustained diastolic hypertension and overt manifestations of cerebral vascular disease. The duration of hospitalization varied from one to 14 years, and the existence of hypertension was confirmed during this period. In several instances the hypertension was of longer duration. All subjects had experienced single or multiple episodes of cerebral thrombosis previously, and 5 of the 8 subjects were mentally deteriorated. In addition, these patients complained of, or manifested, dizziness, weakness in the legs, headaches, staggering, and visual disturbances. For several weeks prior to drug administration, blood pressure determinations were made twice daily by the same nurse using the standard sphygmomanometric procedure. In addition to the usual baseline hypertensive evaluation, studies of cerebral hemodynamics and metabolism were made.

The nitrous-oxide procedure for the determination of cerebral blood flow as devised by Kety and Schmidt[2] and modified by Scheinberg and Stead[4] was employed. Cerebral blood flow, cerebral vascular resistance, and cerebral metabolic rate were calculated as described by the above authors. The mean arterial pressure was read from a damped aneroid manometer attached to a needle inserted in the femoral artery. Blood gas analyses were performed according to the manometric technique of Van Slyke and Neill[3].

After the baseline observations were obtained, Serpasil therapy was instituted, initially 0.4 mg. was given daily in divided doses, increased to 1 mg. after 4 days, and then increased by 0.25 mg. at weekly intervals to maximum blood pressure depression. In several subjects the dosage was still further increased. The patients were maintained for at least 4 weeks on the maximum dose schedule, and the baseline studies were repeated.

Results. Therapy at any dosage level below 1.5 mg. daily was of such

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†Serpasil supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

TABLE 1.—EFFECT OF SERPASIL ON CEREBRAL HEMODYNAMICS AND METABOLISM

		CBF		*CVR*		*$CMRO_2$*		*AVO_2*		*MAP*		*Avg. Blood Pr.*		*Serpasil Dose (mg.)*	
Patient	*Age*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*Effective*	*Maximum*
E. C.	50	39.9	40.4	3.5	3.4	2.3	1.7	5.73	4.20	140	136	170/107	140/75	2.0	2.0
W. T.	71	50.7	50.4	3.2	2.7	3.1	3.7	5.82	7.30	160	138	174/107	141/83	2.0	4.0
B. I.	57	45.5	40.6	2.4	2.6	2.8	2.5	5.62	6.17	120	106	176/105	148/85	1.5	1.5
W. W.	64	45.9	36.5	3.9	3.7	3.3	3.3	7.17	8.95	175	136	196/116	159/94	4.0	4.0
S. C.	59	29.2	32.3	3.8	4.2	2.3	2.1	7.78	6.54	112	136	179/118	133/79	3.0	4.0
A. G.	72	42.5	39.5	3.1	3.9	2.6	1.6	6.05	4.10	136	152	177/97	142/71	4.0	4.0
M. M.	45	50.5	48.3	3.0	3.0	2.2	2.7	4.33	5.66	153	145	161/102	140/82	3.0	4.0
W. B.	61	27.4	35.4	5.1	3.5	1.2	2.2	4.43	6.31	140	125	179/111	111/80	4.0	4.0
								MEAN VALUES							
		41.5	40.4	3.5	3.4	2.5	2.5	5.87	6.15	142	134	177/108	143/81	2.9	3.6

CBF signifies cerebral blood flow in cc./min./100 gm. of brain; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. of brain; $CMRO_2$, cerebral oxygen consumption in cc./min./100 gm. of brain; AVO_2, cerebral arteriovenous oxygen difference in volumes per cent; MAP, mean arterial blood pressure in mm. of Hg; Avg. Blood Pr., average blood pressure in mm. of Hg. C indicates control and E, experimental.

short duration that evaluation of effects other than blood pressure depression was not warranted. A moderate reduction of blood pressure was noted with 1 mg. per day. At higher doses, while there was in several instances an increased hypotensive effect, there was also a concomitant decrease in their responsiveness. If the dose was further increased, no appreciable change in blood pressure occurred but lethargy became more marked, and the patients became greater management problems. The maximum blood pressure depression was achieved with a dosage of from 1.5 to 3.0 mg. per day and averaged 24 mm. Hg systolic and 27 mm. Hg diastolic. The maximum dose administered was 4.0 mg. daily.

There was no improvement in any of the signs or symptoms attributed to vascular insufficiency in any of the patients at the dosage levels studied. With larger doses, the patients who initially showed the most marked mental aberrations seemed to be the most adversely affected. Nasal congestion and diarrhea offered no particular problem, and no significant changes occurred in the hemogram, blood urea nitrogen level, or electrocardiogram.

The cerebral hemodynamic and metabolic data obtained before and during Serpasil therapy are presented in Table 1. Despite the change in blood pressure and mental state, there was no significant change in cerebral blood flow, cerebral metabolic rate, or vascular resistance. The discrepancy between the relatively small fall in blood pressure observed during cerebral function studies as compared to the sphygmomanometric observations is most likely due to failure of the drug to block pressor responses attendant to the procedure.

Discussion. In the present study the doses of Serpasil were admittedly larger than usually employed therapeutically. This was done in order to achieve maximum blood pressure depression and to assure maximum alterations in cerebral hemodynamics and metabolism if such changes were to occur. It is apparent that Serpasil in larger doses had no significant effect on either cerebral hemodynamics or metabolism. It is unlikely, therefore, that the beneficial effects reported with smaller doses result from such changes.

It should be pointed out, however, that the blood flow and oxygen consumption of certain regions of the brain may undergo significant changes without being reflected by the procedure employed, which measures only total cerebral blood flow and oxygen consumption. It is also recognized that changes in the functional activity of the central nervous system need not be accompanied by alterations in total blood flow and oxygen consumption.

It would seem that Serpasil alone in the dosage employed in this study is of little value in the treatment of the hypertensive arteriosclerotic patient.

Summary. Eight subjects with persistent diastolic hypertension and clinical cerebral vascular insufficiency were treated with large doses of reserpine (Serpasil).

Serpasil effected a significant depression of the average blood pressure in all subjects. No concomitant improvement in the manifestation attributed to cerebral insufficiency was noted, and there was no significant change in either cerebral hemodynamics or metabolism.

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CEREBRAL HEMODYNAMIC RESPONSE TO BLOOD PRESSURE REDUCTION WITH PHENOXYBENZAMINE (DIBENZYLINE-688A)*†

By John H. Moyer, M.D.
ASSOCIATE PROFESSOR OF PHARMACOLOGY AND MEDICINE

Harvey Snyder, M.D.
ASSISTANT INSTRUCTOR IN MEDICINE

AND

Sam I. Miller, M.D.
ASSISTANT PROFESSOR OF CLINICAL MEDICINE

WITH THE TECHNICAL ASSISTANCE OF
C. Polk Smith

(From the Departments of Pharmacology and Medicine, Baylor University College of Medicine, Houston, Texas)

Previous observations have indicated that when the blood pressure is lowered in patients with hypertension the cerebral arterioles dilate in a compensatory manner[1,2] and thus maintain cerebral blood flow. Despite the cerebral vasoconstriction that exists in patients with hypertension, the regulation of cerebral blood flow does not appear to be under the regulation of the sympathetic nervous system since stellate ganglionic blockade does not appear to affect cerebral blood flow[4]. However, there always exists the possibility that sympathetic fibers other than those transversing the stellate ganglia may transmit impulses to the cerebral vessels. Phenoxybenzamine (Dibenzyline) is a potent adrenergic blocking agent and when injected intravenously it can be expected to reach all end organs innervated by the sympathetic nervous system throughout the body. In the current study this drug was injected intravenously into patients with hypertension until the blood pressure had been reduced to normotensive ranges and until complete blockade of the vasopressor response to a test dose of norepinephrine was obtained. Observations on cerebral vascular hemodynamics were made before and after adrenergic blockade in order to see if there was any differential response between the vessels in the brain and those in the remainder of the body.

Methods. Cerebral hemodynamic studies were made on 7 patients with severe hypertension. Cerebral blood flow was determined by the nitrous oxide method[5] as previously described[6,7]. All studies were made in the supine position. After suitable control observations were made on the pulse rate, respiration, and cerebral blood flow, phenoxybenzamine (Dibenzyline) was administered by continuous intravenous infusion. A total of 1 mg. per kilogram body weight was placed in 300 cc. of 5% glucose in distilled water. This solution was then infused intravenously at a rate of 4 to 6 cc. per minute, until the blood pressure had returned to normotensive ranges. A test dose of 0.2 mg. of norepinephrine was then given to test for adrenergic blockade. If blockade to the norepinephrine was not complete, the infu-

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TABLE 1.—CEREBRAL HEMODYNAMIC RESPONSE TO BLOOD PRESSURE REDUCTION BY ADRENERGIC BLOCKADE WITH DIBENZYLINE

	Pulse Rate		*Mean Blood Pressure*		*Cerebral Blood Flow cc./100 gm.*		*Cerebrovascular** Resistance*		*Cerebral Oxygen Uptake****		*Hematocrit*			
Patient	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*Jugular Pressure*	*Age*
D. D.†	76	72	148	93	45	36	3.3	2.6	3.0	2.3	40	40	4.0	54
J. S.*	87	92	144	92	56	72	2.6	1.3	3.9	4.1	37	38	7.0	50
N. S.†	100	110	173	105	43	53	4.0	2.0	3.0	3.8	36	36	3.8	43
G. M.†	100	84	168	68	43	21	3.9	3.2	3.7	2.4	45	45	6.8	49
C. J.‡	75	72	108	55	42	25	2.6	2.2	5.3	3.6	42	47	8.0	57
D. T.†	84	80	162	76	48	30	3.4	2.5	3.0	2.2	38	36	—	33
R. J.	76	82	138	82	56	55	2.5	1.5	3.4	3.4	40	39	—	64
Mean	85	85	149	82	48	42	3.2	2.2	3.6	3.1	40	40	5.9	50
Per cent of Control‡‡		100		55		88		69		86		100		
P value<		NS		.01		NS		.01		.20		NS		

* Associated heart failure and diabetes mellitus.

NS $P > 0.30$

† Malignant hypertension.

‡ Disorientation after second cerebral blood flow study.

** Cerebrovascular resistance $= \frac{\text{Mean blood pressure}}{\text{Cerebral blood flow.}}$

*** Cerebral oxygen uptake in cc./100 gm. brain/minute.

C Control

D After maximum reduction and stabilization of blood pressure with phenoxybenzamine (Dibenzyline).

‡‡ Statitical analysis by R. A. Seibert using formula $t = \bar{x}\sqrt{\frac{n(n-1)}{S_{x^2}}}$

sion of phenoxybenzamine was continued until complete blockade was obtained and actual blood pressure reversal (sharp drop in blood pressure) followed the test dose of norepinephrine. The blood pressure was measured by direct arterial manometry. The blocking dose of phenoxybenzamine was usually 0.50 to 0.75 mg. per kilogram body weight. Observations on only 7 patients were made because the degree of blood pressure reduction was too difficult to regulate at the point of adrenergic blockade and there are no effective antidotes to combat the hypotension produced by adrenergic blockade with this blocking agent. The only effective measure, when excessive hypotension occurred, was to tilt the patient in the head-down position. This method was not very reliable at best.

Results. The cerebral hemodynamic effects of blood pressure reduction by adrenergic blockade with phenoxybenzamine (Dibenzyline) are presented in Table 1. When adrenergic blockade was established, there did not appear to be any preferential release of vasoconstriction in the cerebral vessels as compared with the remainder of the body. As the blood pressure decreased, the cerebral vessels dilated, thus reducing cerebrovascular resistance and maintaining cerebral blood flow. However, this reduction in cerebrovascular resistance was sometimes inadequate when blood pressure levels in the low normotensive and hypotensive ranges were obtained and, as a result, cerebral blood flow was depressed. A significant degree of cerebral anoxia was not observed with the reduction in cerebral blood flow in most instances because the oxygen was extracted more completely from the blood flowing to the brain. This resulted in an increase in A-VO_2 (Table 2). However, there was one exception, a patient (C.J.) in whom the cerebral blood flow was sharply depressed. During the control period, oxygen consumption, was particularly high in this patient and when the blood pressure was reduced, the oxygen extraction from the blood was inadequate. As a result, cerebral oxygen consumption per minute ($CMRO_2$) decreased. This was accompanied by disorientation and cerebral depression. Respiration became irregular at the same time. These effects were completely reversible as the drug became less effective and the blood pressure increased.

Discussion. It appears that adrenergic blocking agents affect the cerebral vessels in patients with hypertension in much the same way that other hypotensive agents (ganglionic blocking and centrally acting agents) do. As the blood pressure is reduced, the cerebral vessels dilate in an attempt to maintain cerebral blood flow. However, when blood pressure reduction is quite marked in these patients, vasodilatation is inadequate, which results in a decrease in cerebral blood flow. The brain compensates for the reduction in cerebral blood flow by extracting more oxygen from the blood. However, there is a point beyond which compensation is inadequate and cerebral anoxia with altered cerebral function follows.

A comparison of the response to blood pressure reduction in hypertensive and normotensive patients using different blocking agents is presented in Table 3. There is essentially no difference in response among the various drugs and the degree of blood pressure reduction as well as the pre-existing state of the cerebral vessels (hypertensive, normotensive, sclerotic, and others) appear to be important factors. In patients with hypertension, the blood pressure can be reduced to a moderate degree without affecting either cerebral blood flow or cerebral oxygen consumption. This response was observed in the hypertensive patients who were given dihydroergocornine. However, when the blood pressure was reduced to normotensive levels, the cerebral blood flow tended to decrease, although cerebral

TABLE 2.—EFFECT OF ADRENERGIC BLOCKADE ON CEREBRAL BLOOD OXYGEN AND CARBON DIOXIDE

	Respiratory Rate		*Arterial O_2 Volume %*		*Venous O_2 Volume %*		*Arterial-Venous O_2 Volume %*		*Arterial CO_2 Volume %*		*Venous CO_2 Volume %*		*Arterial P CO_2* mm. Hg*		*Venous PCO_2 mm. Hg*	
Patient	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*
D. D.	21	23	16.1	15.9	9.4	9.4	6.7	6.5	50.3	49.5	56.5	56.4	42	40	34	34
J. S.	25	30	14.7	11.3	7.7	5.6	7.0	5.7	49.0	50.0	55.2	56.5	36	37	30	31
N. S.	22	28	13.1	12.2	6.2	5.0	6.9	7.2	45.0	42.9	52.4	50.7	36	36	33	32
M. G.	14	14	18.5	15.8	10.0	4.6	8.5	11.2	45.7	45.8	53.2	56.2	43	44	38	40
C. J.	33	50	18.8	19.8	6.2	5.3	12.6	14.5	29.0	30.1	33.9	33.6	38	45	—	—
D. T.	20	24	17.2	18.0	11.0	10.7	6.2	7.3	38.2	39.1	44.1	44.2	43	39	—	—
R. J.	18	20	16.0	15.7	10.0	9.5	6.0	6.2	50.0	41.1	50.2	42.1	40	40	—	—
Mean	22	27	16.3	15.5	8.6	7.2	7.7	8.4	43.8	42.6	49.4	48.5	40	40	34	34
Per cent of Control		123		95		84		109		97		98		100		
P Value <		.10		NS		.10		NS		NS		NS		NS		

* Arterial partial pressure of carbon dioxide in mm. Hg
C Control
D After Dibenzyline
NS P>0.30

TABLE 3.—COMPARISON OF CEREBRAL HEMODYNAMIC RESPONSE TO BLOOD PRESSURE REDUCTION WITH VARIOUS AGENTS IN HYPERTENSIVE AND NORMOTENSIVE SUBJECTS: MEAN VALUES

		Mean Blood Pressure mm. Hg		*Cerebral Blood Flow cc./min.*		*Cerebral Oxygen Consumption cc./min.*		*Cerebro-vascular Resistance*		*Arterial P CO_2*		*A-VO_2*		*Number Patients Studied*
Type of Patient	*Drug Administered*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	*C*	*D*	
Hypertensives (severe)	Phenoxybenzamine	149	82	48	42	3.6	3.1	3.2	2.2	40	40	7.7	8.4	7
Hypertensives (severe) (6)	Alkavervir	173	108	57	50	2.9	3.4	3.2	2.3	39	37	5.2	6.9	10
Hypertensives (severe) (1)	Dihydroergocornine	160	122	58	58	3.5	3.6	2.9	2.0	38	39	6.1	6.3	12
Normotensives	Hexamethonium	99	62	57	42	3.2	2.9	1.8	1.5	41	40	5.6	7.2	8
Normotensives	Arfonad	99	57	52	36	3.1	2.8	2.0	1.7	39	41	6.0	8.0	6
Normotensives (3)	Dihydroergocornine	94	78	60	55	3.8	3.5	1.7	1.5	40	40	6.6	6.5	5

anoxia was largely prevented by an increase in extraction of oxygen from the blood flowing through the brain. This is not so apparent when one examines the mean values for the patients receiving phenoxybenzamine and alkavervir (Veriloid). However, when the individual cases are studied, this response is more apparent[1,6]. When the blood pressure in normotensive as well as hypertensive patients is reduced to hypotensive levels, cerebral blood flow is almost universally reduced. However, here again cerebral anoxia is largely prevented by an increase in extraction of oxygen from the blood flowing through the brain.

Summary and Conclusions. 1. Observations have been made on the cerebral hemodynamic response to blood pressure reduction with phenoxybenzamine (Dibenzyline) administered intravenously to patients with hypertension. If the blood pressure was moderately reduced, cerebral blood flow and cerebral oxygen consumption were not affected. However, when the blood pressure was reduced to low normotensive ranges cerebral blood flow was depressed. Cerebral anoxia was largely prevented by increased extraction of oxygen from the blood flowing to the brain.

2. This study offers no evidence for or against adrenergic activity being involved in the regulation of cerebral blood flow. Certainly, there was no evidence of preferential release of cerebral vasoconstriction following the administration of the adrenergic blocking agent, phenoxybenzamine.

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PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

HARRY GOLD, M.D.
PROFESSOR OF CLINICAL PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE

AND

MCKEEN CATTELL, M.D.
PROFESSOR OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE
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THE PRESENT STATUS OF THERAPEUTIC USE OF ENZYMES

BY E. E. CLIFFTON, M.D.
ASSISTANT PROFESSOR OF CLINICAL SURGERY, CORNELL UNIVERSITY MEDICAL COLLEGE; ASSOCIATE, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

(From the Department of Surgery, Cornell University Medical College, and the Department of Clinical Research, Sloan-Kettering Institute, New York, New York)

PURIFIED enzymes as therapeutic agents are in the early stages of development and evaluation. Their potentialities for treatment of many diseases and surgical conditions and as adjuncts in treatment of many others are great and they will have few harmful side effects if properly used. An understanding of the basic mechanism of action of the presently available materials must be established before they can be used in a logical manner with satisfactory results. It would be impossible, in the space available, to cover the subject completely, but a few important basic concepts will be discussed and reference made to more thorough discussions.

The principles of activation of enzymes, the activators available for each enzyme and the inhibitors normally present or developed as a result of the disease being treated or of the treatment itself, must be understood and considered carefully in each case to be treated.

The enzymes, at present in clinically useful stages of development in a relatively pure form, fall into the groups of 1) proteolytic enzymes, and 2) the enzymes which depolymerize hyaluronic acid.

1) The proteolytic enzymes presently available through drug channels, include: (a) Trypsin; a crystalline enzyme, and (b) Streptokinase-Streptodornase (SK-SD) a mixed activator and enzyme product. The enzymes at present in an advanced developmental stage are: (a) plasminogen; the serum profibrinolysin, and (b) several collagenase-containing preparations. Chymo-

trypsin is a crystalline enzyme with which little clinical work has been done.

2) Hyaluronidase is a commercially available relatively pure enzyme which acts on the hyaluronic acid of the intercellular or ground substance.

THE PROTEOLYTIC ENZYMES. There are at least three groups of proteolytic enzymes found in the body fluids or cells whose activities have been carefully evaluated. They are usually in an inactive state, and may be activated to clean up exudates of infections and wounds. Not all are effective under the same conditions.

(1) The cathepsins are tissue proteolytic enzymes[75,166,167,182,225] which are active in an acid medium (about pH 5). The use of acids such as pyruvic and phosphoric acids in debridement of burn eschars is based on this acid activation of the cathepsins[57, 57a,229,255].

(2) The leukoproteases are enzymes produced by the leukocytes and large mononuclear cells, some of which are active at a slightly less acid pH, than the cathepsins and others in an alkaline medium (about pH 8)[16,138,157,196].

(3) Pepsinogens and peptidases are found in the serum but their importance has not been clarified[15,176,177].

(4) The proteolytic enzyme system in which we are most interested, and which has been popularized for the so-called, "enzymatic debridement," is that which functions at an approximately neutral pH.

Active study of this system goes back to the turn of the century when it was observed that blood contained a fibrinolytic material[70,73]. Later it was found that streptococci which produce rapidly spreading infections and liquid exudates produced a material which resulted in the lysis of human clots and fibrin-bearing exudates[263]. It was thought at first that this was due to a lytic material produced by the streptococci themselves, but ultimately it was shown that it was due to a profibrinolysin (plasminogen) present in the plasma which was activated by the streptokinase[47,175]. It has since been shown that certain strains of streptococci produce not only this activator, but at least three other true enzymes, a streptolysin, an enzyme known as streptodornase which causes the depolymerization of desoxyribose nucleic acid, and a hyaluronidase[238,240,264].

ACTIVITY OF STREPTOKINASE AND STREPTODORNASE. Since streptokinase, the activator, is the principal material produced and since fibrinolysis is the most important activity in debridement of wounds, it is immediately recognized that streptokinase and streptodornase will be of greatest value in the presence of the plasma factor (plasminogen) in the exudate. This factor has been shown to vary markedly in exudates and so the activity of streptokinase and streptodornase is unpredictable, unless the exudate is tested for the amount of plasma factor present.

Another limiting factor is the serious fever reaction which may occur when streptokinase and streptodornase are used in closed spaces or on large absorptive surfaces. It was originally thought that this was due to absorption of products of infection or protein breakdown products through the membranes, which were made more permeable as the result of the treatment. At present, it seems most likely that this is due to the presence of pyrogens in the SK-SD preparation.

Streptokinase-Streptodornase (SK-SD) is available in a vial containing 100,000 units streptokinase and approximately 25,000 units of streptodornase. This may be dissolved in 10 to 20 cc. of solution. Since it is known that this material works best at a neutral pH, it is obvious that if the wound is

either very acid or very alkaline that a buffer solution must be used for dissolving the streptokinase and streptodornase.

TRYPSIN. Trypsin is available as a crystalline enzyme prepared from the bovine pancreas[192]. Trypsin is also effective in a neutral medium (optimum pH 8.0), is a stronger proteolytic enzyme than plasmin or fibrinolysin[50,108a, 147] and its activity is more short lived than is that of fibrinolysin[147], since it digests itself rapidly. The advantages of trypsin are that a known amount of active enzyme is used and it will digest necrotic tissue and proteins other than fibrin which may be present in the wound. The factors limiting the activity of trypsin are similar to those for streptokinase. There is an active trypsin inhibitor present in the plasma of all individuals[108]. This is ordinarily elevated in the presence of infections, in postoperative patients, burned patients, and in patients with many other diseases including malignancy and tuberculosis[49]. The elevation usually occurs within 10 days following the trauma or infection, so it is very likely to be at its maximum when trypsin would be used for the debridement of wounds. This anti-trypsin is increased also as a result of the treatment with trypsin[108], which explains the necessity for increasing the amounts of trypsin used from day to day in treatment.

Trypsin is ordinarily furnished in vials containing 250 mg. (250,000 Armour Units) with a vial of buffer solution containing 25 cc., 1 cc. of the solution will contain 10 mg. or 10,000 units. Trypsin is used as a liquid or as a powder if the wound is moist and at a neutral pH. Under ordinary circumstances approximately 50 mg. of trypsin are used for the first application, depending upon the size of the wound. This amount may later be increased gradually to as high as 400 mg. per application. The disadvantages of trypsin, in addition to the presence of anti-trypsin, are:

1. Its irritative effect. This may be decreased by dilution. Occasionally irritation with reddening, inflammation and pain are produced by this material.

2. Possibility of further erosion of partially devitalized tissues[80], although most users refer to studies showing that trypsin does not digest normal cells.

3. Frequent reactions with a shock-like state due probably to the production and absorption of proteoses which produce a histamine like reaction[216,272]. This last reaction may be controlled in part by the use of antihistaminics[81, 280] advised by most authors before the trypsin is applied. Great care must be taken to prevent injection into the blood stream, especially with needle injection of closed cavities. A very small quantity of trypsin injected directly into the circulation may result in sudden death[257a].

CHYMOTRYPSIN. Chymotrypsin is also a crystalline proteolytic enzyme prepared from bovine pancreas. It has been reported to enhance the activity of trypsin in debridement[212a]. It was used in treatment of malignancy following a single report of improvement in a case of far advanced malignancy[146]. Many unpublished studies and two reports failed to support the value of this use[242,283].

PLASMINOGEN. More recently, plasminogen itself in impure state has been separated from human plasma[48,50,144, 213] and from bovine plasma[159] and may soon be available for use in debridement[165,210,249] and perhaps for lysis of intravascular thromboses. It has already been shown to be effective in the lysis of sodium morrhuate clots in animals[51,109].

ENZYMATIC DEBRIDEMENT. If the wound to be debrided is a surface

wound or burn, the solution SK-SD, trypsin, or plasmin may be sprayed on, or placed on the wound as a wet dressing. More recently, a water soluble base has been used to maintain contact for a prolonged time. If used in a deep, dirty wound, or in a cavity connected to the surface by a sinus, a catheter is usually first inserted into the depths of the wound and the material then injected so as to remain in contact for as long a time as possible. If used in a closed cavity, the enzyme may be injected through a needle as for a thoracentesis, or through a catheter used for drainage after aspiration has assured one that the needle or catheter is in the cavity. Great care must be taken that the injection is not into the lung or directly into the blood stream because of the severe general reaction which might be produced with SK-SD or trypsin.

Proteolytic enzymes as crude extracts of animal pancreatic origin were first used clinically by John Hunter to remove slough from wounds. That highly successful if esthetically undesirable method of cleansing foul wounds and resistant osteomyelitic cavities, the maggot[13], apparently depended upon the production of proteolytic enzymes, tryptases, collagenase and others by the maggots[127,155,215,290].

Papain, a proteolytic enzyme active at pH 5 to 6, was reported to be useful in cleaning up sloughing wounds[101]. It was used in conjunction with weak acids, suggesting that the effective factor was the cathepsins, and it was also very irritating to the tissues. Papain activated with cysteine has also been used with apparent success in treatment of burns[61], and as papain and urea in the treatment of chronic otitis media[116,268]. It was found to dissolve thick tenacious mucus and to have definite effect on necrotic tissue, and was reported to be nontoxic and nonirritating.

STREPTOKINASE-STREPTODORNASE. Although streptokinase itself as previously mentioned is not a true enzyme but rather an activator of an enzyme, this combination of materials was the one recently popularized for so-called "enzymatic debridement." It was first used in the chest cavity[239,264a] and many subsequent reports have been written of its effectiveness in lysis of clotted hemothorax[47,69,87,100,172,208,264a] and in debridement or removal of thickened empyema fluid[47,69,93,104,130,266,267,267a]. Actually, this material should be and is almost 100% effective in lysis of clotted hemothorax, because the blood contains large quantities of the profibrinolysin (plasminogen) which is activated by the streptokinase. A few unsatisfactory results have been reported[130]. Under ordinary circumstances, one injection completely lysed an early clotted hemothorax. The fluid must be withdrawn within 12 to 24 hours, or even sooner if there is a great deal of profibrinolysin in the blood, since an irritative effect will be set up, with outpouring of fluid and leukocytes[139] which may cause distress and even serious difficulty to the patient in less than 12 hours. At least one such case with respiratory collapse and hyperpyrexia has been reported[18]. It has been suggested that a small catheter be placed in the pleural cavity[172a], the streptokinase and streptodornase be injected through this, allowed to remain for about 8 hours or less if the patient shows signs of excess fluid formation, and then the catheter be placed on suction for 24 hours. If it be an old thick-walled and loculated hemothorax, more than one injection may be necessary. It is possible that some of the unsuccessful cases[130] were of this type. In one case a clot, occurring in an extrapleural pneumothorax,

was completely lysed and removed with re-establishment of an adequate extrapleural pneumothorax[97]. Good results were also obtained in postoperative conditions following partial pulmonary resections[209] and the complications of surgery[87]. Most surgeons have opposed its use in postoperative cases because of the danger of opening bronchial stumps, which may be closed only with fibrin. From experimental studies[67] and the above clinical results it seems that one need not fear reopening of the bronchial stump if the closure has been adequate and if 2 or 3 days are permitted following the operation before the material is placed in the pleural cavity.

Success has not been as great in the treatment of purulent empyema because of the inconsistency in the presence of profibrinolysin. However, in early thick fibrinous empyema such as pneumococcic and staphylococcic and in early postoperative empyema with the accompanying serum and bloody exudate there is usually sufficient profibrinolysin present to give a good result[93,264,264a,267,267a]. The streptodornase present also causes some liquefaction of the purulent material because of the degradation of desoxyribosenuclease[238, 240,264]. Results are less likely to be satisfactory in lesions over 20 days old or in tuberculous empyemas. However, a good result in a postpneumothorax unexpandible lung of 5 months' duration, where a practical cure after 2 injections with SK-SD was obtained, has been reported[104].

In one series of both chronic empyema and hemothorax, satisfactory results were obtained in only 3 of 7 chronic empyemas, whereas the same investigators had satisfactory results in 20 out of 23 hemothoraces[130]. Two hemorrhages occurred among the 7 cases of chronic empyema and it was necessary to use as many as 10 injections in some patients in order to obtain a relatively satisfactory result[130].

In hematomas or blood clots elsewhere one would expect to have similar success as in the thoracic cavity, and indeed this has been confirmed in cases of blood clots in the urinary bladder[246] and in an interesting case in which a common duct and T tube became blocked by a hematoma[252]. Others have used this material in dissolving the clots in large hematomas with success. Perhaps the use of hyaluronidase or plasmin may be more satisfactory because of the less severe reaction.

In the treatment of chronic infections elsewhere, the same theoretical and practical considerations apparently hold true[288a]. If the material is used in the early postoperative or posttraumatic period when there is serum or blood mixed with the purulent material, one may expect satisfactory results. If used in old chronic abscesses with thick walls after more than a month, one cannot expect a satisfactory result. In abscesses of the feet, SK-SD in conjunction with proper surgical procedures has improved the results of treatment[184]. The SK-SD was injected daily, for 3 to 7 days, through catheters and allowed to remain in contact with the infected wounds for several hours by clamping off blocking catheters. Six of 11 cases showed excellent recovery in 7 to 9 days, and 3 recovered after additional treatment. With SK-SD used in a number of cases of postoperative pelvic abscesses[53], a much smaller tube could be used for drainage and there was a shorter period of fever, of hospitalization, and less severe symptoms of residual disease at follow-up. Healing and closure of posterior wounds following combined abdominal perineal resections[20] and in cases of extra-peritoneal injuries of the rectum[172], have been aided by leaving a catheter in

the space and injecting SK-SD, positioning the patient so that it is maintained in contact with the wound surfaces and then allowing drainage after about 8 to 12 hours[20]. A single case of successful treatment of an amebic abscess of the liver[241], and speedy healing and recovery in infected wounds has been reported[220,259,288a]. Others have reported excellent results in some abscess cavities, but not in others, particularly those due to tuberculosis and actinomycosis[1]. However, another group of investigators obtained good results with control of infection and healing of all wounds and sinuses in 16 of 19 cases of tuberculous empyema (4 cases), lymphadenitis (5 cases), and disease of the bones, joints or tendons (10 cases)[173]. Another author described 5 successful cases out of 8[248].

There have been fewer reports on the debridement of surface wounds, and the results have been somewhat slower than with the pleural cavities and abscess cavities[188,266]. One might expect other enzymes such as trypsin or plasmin to be more effective in these surface ulcers and wounds, since there is usually so little plasminogen present in their exudates. In one series of cases reporting on the use of SK-SD and trypsin in indolent ulcers favorable results were obtained in 11 of 13 with trypsin and 13 of 17 with SK-SD[163]. Other investigators have shown that SK-SD is most successful in patients with moist infected gangrene with fibrinous and cellular exudate[259] and poor in patients with insufficient blood supply, such as arteriosclerotic gangrene and ulcers[171,259].

Although most authors state that no digestion of normal tissue takes place with SK-SD, increased erosion in indolent postirradiation ulcers has been an unfortunate, serious complication[42]. However, good results with rapid drying, decrease of pain, and rapid cleansing of the ulcers and necrotic areas were obtained in a series of cases of radiation necrosis[135], with only one failure among 15 cases and that in an ulcer with cancer in the wall.

TRYPSIN IN ENZYMATIC DEBRIDEMENT. Trypsin has been used in practically the same condition as SK-SD, and from most reports with great success. Considering the known activities of trypsin and plasmin[49] less success would be expected with trypsin in hemothoraces and hematomas because it is relatively less fibrinolytic than plasmin and the plasminogen is already a part of the clot where it is more active in lysis. Only a few cases of satisfactory lysis of hemothoraces and hematomas have been reported[72,186]. Theoretically, one would expect greater activity of trypsin in cleaning up infected cavities and wounds, since it acts on more proteins than does plasmin or plasmin and streptodornase.

In empyema, trypsin has been said to be very effective in those of up to 3 to 4 weeks' duration[212,217]. However, in 9 patients with chest conditions the results were not satisfactory in the experience of another group[45], possibly because of the long duration of the empyema. In the treatment of necrotic sloughing wounds, in infected wounds and on leg ulcers the treatment has been particularly satisfactory, either as a wet dressing or as a powder sprinkled on those with moist secretions[55,212a,223]. Most wounds respond in a period of 5 to 8 days and only a few take more than 14 days to become clean and prepared for grafting or begin healing. Even necrotic muscle is digested in cases of massive wounds or with gas gangrene and there is an outpouring of serum and leukocytes which are thought to improve the cleansing of the wound and healing[211]. More recently, a combination of trypsin and chymotrypsin has been used with

markedly increased proteolytic effect both *in vitro* and also *in vivo*[212a]. In dirty postoperative wounds, such as those following operations in the anorectal region, more rapid cleansing and healing has been obtained[34].

INTRABRONCHIAL LYSIS OF TENACIOUS MUCUS. For liquefaction and free expectoration of thick tenacious mucus, several enzymes have been tried. Papain might be expected to have great activity because of its mucolytic effect, and indeed it was shown to be very effective, but too irritating. SK-SD has been tried, with success in a few cases[66,174,181]. Trypsin as an aerosol inhalation with oxygen, in a concentration of 50 mg. per 1 cc., 3 or more times per day, has been reported to be very effective[153,183,200,217,270,273]. Good results were obtained in 13 of 17 cases with marked increase in fluidity in 10 of 17 in one report[289]. It has also been effective with tracheotomy[251]. It is possible that the nonspecific irritating effect with the outpouring of the liquid and leukocytes[92,211] may be the important factor in the use of this material. Only one author[66] reported on the use of both SK-SD and trypsin, and this only in a single case where SK-SD was used first with limited success and then trypsin gave excellent results. A combination of trypsin and pancreatic desoxyribosenuclease has been used with success[92], but with frequent complications of cough, hoarseness, aphonia or hemoptysis, and nine patients refused further treatment. Desoxyribosenuclease prepared from ox pancreas has been used alone, using 0.5 mg. per cc.[7], for liquefaction of the purulent exudate in sputum with satisfactory results, especially in bronchiectasis and other diseases with thick mucopurulent exudate[7]. With trypsin, irritation of the mouth, larynx, trachea and bronchi with marked hoarseness has not been uncommon. Several ways of preventing this have been tried, including washing out the mouth immediately after using, and the use of petroleum jelly in the nose.

BURNS. The most serious unsolved problem of burn therapy is the debridement of relatively old burn eschars. Papain in a 2% solution activated by cysteine hydrochloride and with sodium salicylate 8% was reported to be useful, causing lysis in 10 hours in one case and 25 hours in another[61]. Because of the nature of the eschar, SK-SD and even trypsin would not be expected to be very successful, and indeed they have not been, even with cross hatching[55,265]. However, an impure pancreatic extract containing trypsin was reported to be successful[254]. Crystalline trypsin has been found to increase the speed of separation of the eschar but this has not seemed to be of sufficient degree to justify extensive use of the material[55a,252,285]. The lysis of the eschar in one report[284], occurred in 10 to 15 days with trypsin, as compared to 21 days in the controls. One would expect that a special type of enzyme, a collagenase, would be necessary for the digestion of burn eschars, since they are made up primarily of coagulated collagen. At the present time these enzymes are still in the stage of development, but they are mentioned because of their great promise[132,191]. Reports have been made of the effectiveness of these impure materials on the separation and lysis of the burn eschars in as short a time as 24 to 48 hours[55a,132]. The effect of acid gels in lysis of eschars has already been noted[57,57a,229,255].

THROMBOPHLEBITIS, PHLEBOTHROMBOSIS AND ARTERIAL THROMBI. Only trypsin has had a sufficient clinical trial to make any statement as to its effectiveness in these conditions. It would not be expected that intravenous trypsin could be used to lyse clots since it

produces a shock-like state in small doses[257a] and actually produces clotting of blood[26,85,129,257]. Furthermore, the serum inhibitor would quickly inactivate the small amounts used clinically[237]. However, it has been reported to be fibrinolytic and to produce a marked improvement in thrombophlebitis, phlebothrombosis, coronary occlusion, thromboses of retinal vein and other diseases, presumably by lysis of clots when injected slowly intravenously (10 to 15 mg. trypsin per 100 cc.)[136,136a,136b]. The mode of action is not clear, and the theory that trypsin activated the plasminogen in blood seems doubtful, though theoretically sound[145,152]. Others[94,150] found no lysis of thrombi by intravenous injections, but they did observe improvement of the inflammatory conditions. It does cause a decrease in fibrinogen, prothrombin and thrombin which may prevent further thrombus formation[136]. One case of pulmonary embolism with intravenous trypsin therapy has been reported[235]. Subsequent reports have indicated that the same beneficial effects in inflammatory conditions have followed the intramuscular injection of 1 to 2 cc. of trypsin (2.5 mg. per cc. sesame oil)[94].

Experimentally SK-SD, in very large doses over a long period of time, has been used to lyse thrombi in rabbits' ears[140]. Plasmin, profibrinolysin activated by small amounts of SK-SD, has been shown to be effective in lysis of sodium morrhuate clots[51,108].

THE USE OF ENZYME IN PREVENTION OR LYSIS OF ADHESIONS. SK-SD might be expected to be effective in the prevention and dissolution of early peritoneal adhesions. In experimental work in dogs and other animals, SK-SD failed to give any clear-cut results[288], but one important factor, that the animal profibrinolysin is not activated by streptokinase[50a], was not taken into consideration in these experimental studies. Prevention of adhesion formation in rats has been reported[162]. One case of clinical use of SK-SD in a postoperative obstruction, following operation for tuberculous salpingitis, in which 1 cc. of (SK-7400 units, SD 85 units/cc.) was used every 3 hours for 3 days and then every 6 hours for 5 days, was successful[274]. Personal experience with 3 cases has been satisfactory[49a].

Experimental studies on the use of hyaluronidase in prevention of peritoneal adhesions indicated that it did markedly decrease the formation of adhesions when talc was used[46,56] but not with crushing injury of the bowel[260]. In another group of animals in which intraperitoneal injections of fats were made there were numerous adhesions in the controls, but with hyaluronidase-treated animals there were no adhesions[222]. One group of authors reporting on the use of material in human patients found that in 12 of 14 patients treated with hyaluronidase there was no reformation of adhesions[56].

TUBERCULOUS MENINGITIS. Perhaps one of the most hopeful suggested uses of SK-SD was in treatment of tuberculous meningitis[43,43a]. It was thought that SK-SD would lyse the fibrinous exudate found at the base of the brain, which prevented intrathecal streptomycin from reaching the diseased area. Marked improvement in results with its use has been reported[44,187]. These results have not been confirmed[84,160,160a]. The reason for these differences in results is not apparent in the articles cited, but it has since been shown[96] that very high doses of SK-SD are necessary to activate the cerebrospinal fluid, since there is only a small amount of the proenzyme present. In another experimental study with monkeys, it was shown that there was an outpouring of leukocytes and proteins with the injection of SK-SD into animal subarach-

noid space and that the heat-inactivated material had the same effect[115]. At least one death with a severe febrile reaction to over 106° F. and coma following use of SK-SD has been reported[65], but this patient was febrile and semicomatose at the time of the injection of the material. Further study of this material has probably been abandoned because of the effectiveness of other drugs in cerebrospinal tuberculosis.

HYALURONIDASE. The therapeutic activities of hyaluronidase are based primarily on its spreading effects in tissues[83]. This spreading effect is due to the depolymerization of the hyaluronic acid which is present in the ground substance found between all cells in the body. Obviously any enzyme which will liquefy or make less solid this intercellular substance will aid in diffusion of materials to and from the cells. Hyaluronidase itself is produced by microörganisms, leeches, and is found in the venom of poisonous snakes and insects, in spermatozoa and the mammalian testis[83a]. The materials used clinically are produced primarily from the bovine testis. Hyaluronidase for clinical use is furnished as a dried powder which is free of pyrogens and which is readily soluble in water or saline. In the dry state it is stable indefinitely, and even in solution it remains stable for a long time, if sterile. When dissolved in procain solution it is stable for at least 2 weeks at room temperature and for a longer time at 5° C. The activity is expressed in turbidity reducing units (TRU) or viscosity reducing units (VRU) and 1 TRU equals approximately 3.3 VRU.

The early preparations of hyaluronidase occasionally produced foreign protein reactions and sensitization. The presently available material is relatively pure and at the present time reactions of any type are extremely rare[226]. There were no reactions in 150 skin tested patients in 1 series[137] and 3 reactions of an allergic type in a series of over 500 diagnostic and therapeutic nerve blocks in another experience[179]. For those interested in the mechanisms of action and the chemical properties of this material and its inhibitors, a complete review is available in a symposium in the Annals of New York Academy of Science, **52**, 943 to 1196, 1950, and references [83b] and [170].

Several factors must be taken into consideration in clinical use. These include the presence of inhibitors in the serum[76,78,111,112,178,261,271] and the effect of increased pressure of the fluid on the spreading factor[149]. It has been shown that with increased volume of fluid and increased pressure the spreading effect is much increased[119] and it is more effective in tight turgid tissues where the initial resistance is high and less effective with loose skin with low resistance such as in the aged[118]. The activity of hyaluronidase is also influenced by steroid hormones, a factor of importance not only where ACTH or cortisone are used but also in the stress conditions in the patient[195,230,232,233]. Salicylates also inhibit its effect[77,110]. Since hyaluronidase is produced by certain microörganisms and is thought to be an effective factor in the spread of these particular infections[169,169a,185], there may be fear of spreading infections with its use. It has been shown to spread tuberculous infection when acid-fast organisms are injected locally with hyaluronidase but not in general disease[63]. Actually the effect of the material on spread of infection depends upon the relative concentration of the organisms and of the hyaluronidase[83a]. Other authors have indicated that hyaluronidase has an effect on bacteria which enhances their destruction[219,278] and that hyaluronidase actually increases phagocytosis of microörganisms

by the leukocytes[161]. *In vivo* in human patients it has been shown that hyaluronidase modifies the inflammatory response by eliminating edema and causing greater spread[102]. Another field in which there has been some evidence that there might be contraindications to the use of hyaluronidase is in the presence of malignancy. In experimental work on the effect of hyaluronidase in and on malignancies, there has been no common conclusion[29,54,103,231,245].

CLINICAL USES. Two reviews of the clinical uses of hyaluronidase have been published previously[31,228].

IN HYPODERMOCLYSIS. The first suggested clinical use of hyaluronidase was in hypodermoclysis[224] and this remains undoubtedly the most commonly accepted clinical use of this drug[12,33]. It is particularly useful in infants where intravenous therapy is so difficult[27,35,52,59,60,98,114,128,137,226,226b,227,228,276]. The rapidity of absorption is increased almost to equal that of the safe spread of infusion in infants[226b], with 250 to 300 cc. of solution given within 80 minutes, as compared with 150 to 180 minutes in the control. The danger of slough from pressure of unabsorbed fluids is prevented, and the area can be used again in a short time[226b]. In adults, it is particularly useful in those who have had long-drawn-out diseases with damage to veins from frequent infusions or thromboses[2,28,68,74,118,124]. It has been observed that with clysis with hyaluronidase in the subcutaneous tissue the fluid absorption is increased 12-fold over the control[118], and that with glucose the glucose curves almost equalled those with venous infusions[74], but was much less effective with the clysis into the muscle.

Where necessary, other fluids besides electrolytes and glucose may be given by clysis using hyaluronidase, without producing the serious symptomatology, such as pain, which occurs without it. Plasma proteins have been shown to be absorbed 1½ to 3 times as rapidly with the enzyme as in controls[14] and plasma has been shown to be absorbed almost as rapidly as nonprotein solutions[98,106,226,228]. Protein hydrolysate with dextrose has been given by clysis with this method with good results[89]. Whole blood absorption was much less satisfactory, causing only a slight rise in hemoglobin in 4 cases, and blood should be given this way only where it is absolutely impossible to give it by other means[226,228]. Absorption of fat emulsions, in both animals[222] and patients, was found to be comparable to that with intravenous infusion, without local tissue reaction or residual collections of fat[236].

Hyaluronidase in clyses is used either as a single dose before, or into the tubing in the early part of the clysis, using 150 TRU for a clysis of 1,000 to 2,000 cc., or is mixed with the clysis using approximately 10 TRU per 100 cc. of solution. Since it has been shown that the rate of diffusion of fluid with hyaluronidase is increased by pressure[35,118,119,119b], it is logical to apply and maintain pressure by elevation of the clysis bottle. It is possible to use the same area for a second time within 24 hours because of the failure of reconstitution of the hyaluronic acid barrier in that period of time[119a,226].

Contraindications to its use include low serum proteins, congestive heart failure, venous stasis and shock[226b], primarily because with the rapid absorption, the same difficulties may follow as with too rapid infusions. Under certain conditions, the fluid will be diffused but not absorbed by the blood stream until later, with resultant overloading. With certain electrolyte abnormalities there may be further harmful side effects because of equalization of the electrolytes with the fluid in the

extravascular pool produced, especially if this be glucose or plasma. Sodium depletion has been reported in such patients[68], and has also been shown in experimental animals[250].

ABSORPTION OF DRUGS. A similar application of hyaluronidase is to enhance the absorption of medications, especially those which must be given in large quantities and which are painful when given subcutaneously. It has been used in the injection of contrast substances for visualization of the urinary tract or gallbladder, for the absorption of sera such as measles serum[98] and for drugs such as penicillin[180] and heparin[26] which must be given continuously in quantity, and where the intravenous route is desirable but not available. Excellent pyelograms have been obtained[31,35,39,40,126,194]. For pyelograms, 150 TRU in 1 cc. of solution are injected into the area to be used followed in 10 minutes by the dye and massage. As little as 30 TRU in 5 cc. of 1% procaine has been used with success[31]. Using hyaluronidase with subcutaneous injection of PAS in tuberculosis[95,97] it was found that the PAS concentration in the blood was comparable to intravenous injection and 2 or 3 times that obtained with the usually tolerated oral doses, with a delayed peak after 6 hours suggesting a depot effect[95].

LOCAL ANESTHESIA. The use of this enzyme in local anesthesia has many advantages including: less ballooning and distortion of tissues, an increase in diffusion of the anesthetic with a wider area of more complete anesthesia and a more rapid induction, with less agent required. In addition, there is usually less postoperative edema and ecchymosis. The disadvantages include a shorter duration of anesthesia, and some increased toxicity especially with the more rapidly absorbed anesthetics, if the standard amounts of anesthesia are used. Animal experiment has not confirmed the latter[234]. The combination of local anesthetic with hyaluronidase has been found to be particularly effective for pudendal block in obstetrics[17,79,82,107,121]. This advantage in addition to those mentioned above is due particularly to the fact that the anesthesia need not be placed directly on or into the nerve. With caudal anesthesia, however, there has been no apparent increase of effectiveness with hyaluronidase[199].

The combination of procaine with hyaluronidase has been found to be useful in local anesthesia for reduction of fractures[262], in dental surgery[86,158,258], in tonsillectomy[120] and in nasal plastic surgery for rhinoplasty and submucous resection[64]. Local anesthesia in ophthalmology has been made more satisfactory because of the decompressing effect, less ballooning of the tissues and good general paralysis of the extraocular muscles with one injection[10,41,142,151,275]. Mucosal absorption is increased in surface anesthesia[133], and smaller amounts of anesthesia can be used, but one must beware of increased absorption with serious toxic reactions.

In general, 150 TRU of hyaluronidase are injected before the local anesthetic, or the hyaluronidase is mixed directly with the anesthetic in a concentration of about 150 TRU to 100 cc. of procaine. For dental work the usual dental cartridges may be used by removing a small amount of anesthetic and adding the hyaluronidase in the quantity needed.

Related to its use in anesthesia is the use of hyaluronidase in the treatment of acute strains, sprains, myositis, bursitis and arthritic disorders[9,99,183].

DISPERSION AND DISSIPATION OF FLUIDS AND EDEMA. The reabsorption of collections of blood and fluid is hastened in most instances by injections of hyaluronidase, frequently with procaine. It

has been found to be especially useful in joint spaces, especially in hemophilia[183a] and traumatic hemarthroses[99]. In large joints, 1000 to 1500 TRU diluted in procaine are ordinarily used and pressure is maintained by wrapping tightly with an elastic bandage. One treatment is usually sufficient but a second one in 24 hours is sometimes necessary. A few reports of the use of hyaluronidase in hemothorax and hydrothorax have indicated more rapid absorption when the collections are relatively fresh[3,4,203]. However, with the excellent results with aspirations only, its usefulness seems doubtful.

In early hematomata and traumatic edema[31], rapid resorption occurs. With or without local anesthesia in the treatment of fractures, it has been found to assist in their early reduction by permitting better palpation and manipulation[183] following the resorption of the edema fluid. In severe fractures of the forearm with subfascial hematoma and edema the dispersion of the fluid and blood prevents fibrosis and contractures, as well as myositis ossificans in the muscles[99]. In the occasional complications of leakage of irritating substances from infusions it has also been very effective in speeding resorption and relieving pain[31,113,179a].

The resorption of excess fluid from tissue has also been greatly facilitated by hyaluronidase. Pretibial myxedema responds well[24,105,218,279], especially when combined with pressure dressings. Paraphimosis is reduced very quickly (12 to 20 minutes) without pain or necessity for surgical intervention[91,207,286]. In generalized scleroderma, hyaluronidase by iontophoresis is said to be effective[202] and mucinous infiltrations of the skin respond to injection[24].

DISEASES OF THE EYE. The use of hyaluronidase in controlling edema, exophthalmos and inflammatory lesions such as keratitis in ophthalmology have been very thoroughly evaluated[41,71,142,151,154,275]. In the eye the amount of hyaluronidase used is much smaller, usually about 5 TRU per cc. of solution, frequently procaine 1%. This has been found to be very effective in keratitis[71], glaucoma which is markedly decreased in 15 minutes (according to one author[151], but less satisfactory in other hands[154]), iritis, corneal ulcers, hypopyon, pterygium, and posterior synechiae among others[41,151].

OTHER USES. Many other therapeutic uses of hyaluronidase have been suggested, but most of these remain controversial and less accepted than the above. In many instances, but a single report can be found in the available literature concerning these special uses.

In the treatment of chronic ulcerations such as those following varicose veins it has been thought that hyaluronidase alters the ischemic fibrotic tissues, so that permeability to circulation and thus nutrition increases. Improved healing of such ulcers has been reported with the use of hyaluronidase alone by iontophoresis[90,202a] and with the use of hyaluronidase in conjunction with plasmin and antibiotics[249].

In thyrotropic exophthalmos there was some hope that it would decrease the protrusion of the eye, since it did have an effect on experimental exophthalmos in guinea pigs[193], but in at least one human case there was an actual increase in the proptosis and edema following injection of hyaluronidase[141], but in this case a rather large quantity of less pure material, 250 VRU in 3 cc. of 2% procaine was used.

Because hyaluronidase is present in the testicles and in the spermatozoa, it was thought that lack of the enzyme was a factor in certain cases of sterility[282,287]. The fact that hyaluronidase containing sperm filtrate increased the fertilization percentage in rabbits[221]

was further evidence for a trial of this material in humans. Only one author however, has reported increased fertility in those patients treated with hyaluronidase[148]. Others have failed to find any significant change in rate of fertility[243,256].

The status of the effect of hyaluronidase on the formation of urinary calculi is also in doubt, despite several reports concerning its effect on the colloids of urine[36,36a,37,37a,38]. Certain types of kidney stones were reported to be prevented from reforming by the injection of hyaluronidase[38a]. This has not been confirmed by other urologists, to our knowledge, and indeed an increase in stone formation was recently reported[204]. There has been no *in vivo* support for the observed fragmentation of stones *in vitro*[189] and stone formation has not been prevented in animal experiments[123].

Hemostasis in transurethral resections by the preliminary injection of a solution of hyaluronidase, adrenalin and procaine into each lobe of the gland has been reported in a well controlled series[19]. Hyaluronidase has also been said to be effective in treatment of toxicosis of pregnancy[201] and in the absorption of myxomatous material produced by a mesothelioma of the pleura and peritoneum[253]. It has been said to heighten the activity of BCG vaccine, with a 61% early take and a more active response later in those receiving hyaluronidase, as compared with 35% in the controls[23]. Keloids have been treated by injection alone[30] and in preparation for surgery[62], using 100 or 150 TRU dissolved in 1 cc. of distilled water[30] or 2% procaine[62] to infiltrate the entire keloid area. Eight to 12 treatments caused softening, relief of itching and pain, and a wrinkling of the keloid. There were no significant recurrences in 26 cases[62]. Combination of ACTH and hyaluronidase has been found to be helpful in relieving pain and itching in keloids in the hands of other investigators[58].

In infections of mucosa-lined structures, such as the nose and sinuses, increased penetration and absorption of antibiotics has followed the use of hyaluronidase[12,52,247]. It has also been used in lung infections both in suppurative disease with antibiotics for treatment[149] and to enhance the spread of antibiotic in tuberculosis[88].

Summary. It is fair to say that when used in conjunction with good medical and surgical principles, including the use of antibiotics, these enzymes are a very useful addition to our armamentarium. Streptokinase-Streptodornase is most useful in hemothorax, hematomas, in thick empyema and in abscesses, wounds or ulcers containing plasminogen. Trypsin will be most useful in debriding early chronic abscesses, ulcers and wounds and for clearing the respiratory tract of thick secretions. Its use in thrombophlebitis and related conditions is still controversial. Hyaluronidase will increase the speed of absorption of clyses and drugs, the resorption of excess fluids and blood in the tissues, and the effectiveness of local anesthesia.

There are many other suggested uses of these enzymes which may be proven to be satisfactory, and new enzymes now in process of development may be found very useful especially in treatment of burns (collagenases) and vascular thromboses (plasmin).

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RADIOLOGY

UNDER THE CHARGE OF

DAVID M. GOULD, M.D.

ASSOCIATE PROFESSOR OF RADIOLOGY
THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL

AND

ROBERT D. SLOAN, M.D.

ASSOCIATE PROFESSOR OF RADIOLOGY
THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL
BALTIMORE, MARYLAND

ABDOMINAL AORTOGRAPHY

BY DAVID M. GOULD, M.D.

AND

JAMES K. V. WILLSON, M.D.

(From the Department of Radiology, The Johns Hopkins University and Hospital, Baltimore, Maryland)

IN recent years abdominal aortography has cast a new light on diseases of the abdominal aorta, its branches and the organs supplied by its branches[10, 110, 113]. The simplicity, accuracy, and relative safety of the method lends itself to ever more frequent employment in problems involving the abdominal arteries and the circulatory status of certain organs[46]. Abdominal aortography, in common with angiocardiography and cerebral angiography, is a dynamic Roentgen method which demonstrates the lumen of the vascular system by the injection of radio-opaque contrast substances into the circulation. It is an elegant morphologic approach to diagnosis with many physiological implications.

The rapid advances in vascular surgery, the intrepid use of larger vascular grafts or synthetic plastic materials for reconstruction, have given impetus to abdominal aortography for exact morphologic diagnosis. To the surgeon, the method is indispensable in planning a procedure. Is an operation necessary? Is it possible? Should a conservative or radical attack be made? Is it better to attempt exact anatomical restoration or would a palliative procedure be more discreet? How successful has the operation been? These and other questions may often be resolved by abdominal aortography.

History. It is interesting to note that abdominal aortography was neither initiated nor developed by vascular surgeons or radiologists. Reynaldo dos Santos, a Portuguese urologist, in 1927, pioneered the method clinically. His first reports of a series of cases appeared in 1929[41, 42]. It may be recalled that about the same time the neurosurgeon Egas Moniz, also Portuguese, did his monumental work on cerebral angiography. There is little doubt that dos Santos was inspired by the work

of Egas Moniz. Between 1929 and 1935, dos Santos performed 431 transvertebral abdominal aortograms[40]. Notwithstanding the preponderant use of sodium iodide and Thorotrast he concluded that his method was quite safe. For the next decade, abdominal aortography was used sporadically in the major clinics of Europe[99].

In America, due to experiments on dogs by Henline and Moore[64] in 1936, abdominal aortography fell into disrepute. These workers claimed that the method was hazardous since permanent vascular damage and death was the end result in many of the dogs. Dos Santos tried to refute the implication that the method was hazardous for human beings by pointing out that canine and human physiology were quite different[2,22]. Nevertheless it was not until 1942, that the American urologists, Nelson, in Washington and Doss, in Texas, made intensive clinical studies of abdominal aortography. Now the pendulum has swung in the opposite direction and since this time, the method has become increasingly popular with many enthusiastic advocates.

HISTORICAL LANDMARKS IN THE DEVELOPMENT OF ABDOMINAL AORTOGRAPHY.

1896: Three months after Roentgen discovered the Roentgen ray, Haschek and Lindenthal (Germany) accomplished the first arteriogram by injecting radio-opaque Teichman's mixture into the artery of an amputated arm.

1918: Cameron[16] (U.S.A.) announced that iodide molecules were opaque to Roentgen rays. Clinical arteriography was then made possible.

1923: Berberich and Hirsch[8] (Germany) injected strontium bromide into the vein of an arm and hand in cadavers.

1923: Siccard and Forestier (France) used Lipiodol (iodized poppy seed oil) to inject vessels in patients[108,109].

1924: Brooks[15] (U.S.A.) injected 50% sodium iodide into the femoral artery of a patient.

1927: Moniz (Portugal) developed cerebral angiography using Thorotrast.

1929: Dos Santos[41] (Portugal) pioneered translumbar abdominal aortography.

1937: Castellanos[17,18] (Cuba) performed first counter-current abdominal aortogram by injecting the femoral artery.

1941: Fariñas[51,52] (Cuba) performed abdominal aortography by passing a catheter by way of the femoral artery.

1942: Nelson[91-93] and Doss[38] working independently popularized abdominal aortography in U.S.A.

Clinical Applications and Diagnostic Features. Abdominal aortography is the method par excellence for the demonstration of vascular abnormalities of the aorta and its branches. Congenital anomalies, aberrant vessels, ectopic vessels, arteriovenous fistulae, aneurysms, thrombi, emboli[82], stenoses, occlusions, Leriche Syndrome, collateral circulation, atherosclerosis and thromboangiitis obliterans are demonstrated in a detailed and frequently definitive manner.

The kidney lends itself particularly well to analysis. Much information can be gained by aortography concerning such conditions as aplasia, hypoplasia, aberrant vessel, ectopia, duplication, horseshoe kidney, urinary stasis, hydronephrosis, ureteropelvic obstruction, calculus, tuberculosis, polycystic kidneys, cyst, neoplasm, infarct, and the "Goldblatt" kidney.

From the vascularity, inferences can be drawn concerning the status of certain abdominal and pelvic organs and structures. Diseases of the spleen, liver, adrenal, ovary, uterus, bladder, paraaortic and retroperitoneal tissues are recognizable.

INTRINSIC VASCULAR DISEASE. Since the arterial lumen is graphically shown by the aortographic method certain morphological states are easily demonstrated. Meager diagnostic acumen is needed to determine arterial patency, dilatation, obstruction, or tortuosity. The recognition of aberrant or ectopic vessels presupposes an intimate knowledge of vascular anatomy.

Arteriovenous fistulae[114] may be either congenital or acquired. In both types usually an enlarged artery is seen feeding varying numbers of huge venous channels. The opaque medium tends to puddle in the dilated draining veins. Of course, clinically bruits or thrills may be present locally or cardiac failure may supervene.

Aneurysm. Generally the diagnosis of aneurysm is not difficult[5,125]. However, it should be pointed out that a large saccular or even fusiform aneurysm may be more or less filled with clot[13]. Thus the true size of the aneurysm will not be shown by aortography. Frequently calcification in the outer wall of the dilated vessel allows the appreciation of the actual size of the thrombus formation. If no calcification is present it is possible to combine aortography with presacral retroperitoneal pneumography[68] to delineate both the lumen and the outer wall of the aneurysm. Often the bulk of the aneurysm sac or erosion of the lumbar vertebrae can be seen on a plain film of the abdomen.

Arterial Occlusion[95,96,103]. Occlusion, whether it be due to embolization or thrombus formation, can be accurately demonstrated[47,88]. It is important to attempt to analyze the collateral circulation and also the length of the obstructed segment. Sometimes the length of the occlusion may be determined from the distance between the proximal opaque material, flowing with the current, and the distal opacification filling the artery in a countercurrent manner by collateral circulation.

The Leriche Syndrome[2,74,75,112]. This syndrome is characterized by: 1) Impotency due to impossibility of erection; 2) extreme fatigue on walking, not necessarily intermittent claudication; 3) considerable muscular atrophy; 4) ivory blanching of the legs on elevation; and 5) disappearance of pulsation and oscillation.

A period of compensation by collateral circulation may exist for 10 years or more. It is followed by a terminal stage at which time the patient is unable to walk and has severe pain with cyanosis and edema. Painful gangrene and death may be the outcome[90].

The aortogram reveals obstruction of the aorta by a saddle thrombus just above the aortic bifurcation. The aortic obliteration usually commences with iliac thrombosis. At first, it is unilateral and then becomes bilateral by propagation of the thrombus in a retrograde fashion. Thrombi may originate in the aortic spur. According to Leriche[76], thrombosis may reach the inferior mesenteric artery but rarely extends to the renal artery. Naturally when both renal arteries are involved, the loss of renal function is incompatible with life. With a block at the aortic bifurcation, greatly enlarged lumbar arteries are frequently seen acting as collaterals. Occasionally the inferior mesenteric artery will be seen anastomosing with branches of the hypogastric artery. A block situated between the superior and inferior mesenteric arteries dilates the natural collaterals between these vessels. In a higher aortic block, the collateral circulation is between the internal mammary and inferior epigastric arteries.

As recently as 1948, Leriche[77] envisioned resection and grafting of the obstructed segment [65,118]. However, up

to that time palliative procedures such as amputation and sympathectomy were used. Now it is technically feasible to resect the aortic bifurcation or other portions and replace the diseased structure with a homologous graft.

Atherosclerosis[78]. An early finding in atherosclerosis is elongation of the artery followed by dilatation and then tortuosity. Narrowing occurs later. In many cases the aortogram reveals irregular plaques which may or may not be calcified. These plaques can be seen protruding and sometimes encroaching on the lumen[26].

Thromboangiitis and Arteritis. It is not usual to see elongation, dilatation and tortuosity in this condition. More often there appears to be a concentric, regular narrowing of the arterial lumen. The lumen may be finally obliterated and the vessel becomes a fibrous cord.

Para-Aortic Tumor. One must also consider extrinsic pressure defects caused by masses contiguous to the aorta or its branches. Various tumors such as lymphoma, ganglioneuroma, metastatic seminoma and neurofibrosarcoma have been observed to exert this effect.

Diseases of the Kidney[127]. The complexity and intensive study of the kidney diseases by aortography almost warrant a special subdivision concerning the renal arteriogram[94]. As a rule the kidney circulation is beautifully demonstrated whenever the injection is made at the levels of the 12th thoracic or 1st lumbar vertebrae. The renal arteries arise from each side of the aorta immediately below the superior mesenteric artery. Before reaching the hilus of the kidney each artery divides into 4 or 5 branches. Each renal artery gives off a small inferior suprarenal branch. One or two accessory renal arteries are frequently found more commonly on the left side. Usually they arise from the aorta above or below the main renal artery. Instead of entering the kidney at the hilus, they usually pierce the upper or lower pole.

Developmental Anomalies of the Kidney[31,32,107,117]. Aplasia, hypoplasia, aberrant vessels, duplication, horseshoe kidney, and ectopic kidneys have been recognized. In aplasia, no renal artery is seen. In hypoplasia, the artery is small and has few branches. Aberrant vessels if patent can be seen and often give rise to hydronephrosis. In duplication of the kidney two separate vascular networks are seen. Although one renal artery has been noted to supply a horseshoe kidney, usually two or more arise from the aorta. The artery for an ectopic kidney may arise anywhere from its normal position to the iliac vessels.

In tuberculosis of the kidney the aortogram may be of great aid[12,130]. Retrograde pyelography is often impossible or contraindicated because of acute inflammatory changes. Generally the chronic tuberculous kidney is contracted and relatively avascular. Weyde[129] believes that focal areas of tuberculosis can be recognized in one kidney so that partial resections can be planned under cover of specific antibiotic and chemotherapy much as is done with pulmonary tuberculosis.

Hydronephrosis. In any case of urinary stasis, hydronephrosis[79] may result. The ureteral block can be acute or chronic, complete or incomplete, either intrinsic or extrinsic. Among the various etiologies may be mentioned congenital bands, high ureteral insertions, malrotation of the kidney, diaphragms, membranes, aberrant vessels[132], primary or metastatic neoplasms, infections, and calculi.

The excretory urogram is usually the initial study but poor visualization by no means equals poor function. Retrograde pyelography is often contraindicated because of the danger of pye-

lonephritis and cortical abscess formation. Doss[37] feels that before sacrificing a hydronephrotic kidney the arterial configuration of each kidney should be carefully worked out. His dictum is "The organ is no better than its blood supply." If the vascularity is good every effort should be made to save the kidney even though the renal cortex is markedly thinned. Aortography in hydronephrosis with chronic infection usually shows the vessels to be spaced widely apart. They are fewer in number and the arterial supply of the renal parenchyma is decreased.

Polycystic Kidneys[106]. Smith[116] states that in this condition there is a spreading out of the vessels as they curve around the avascular spaces; there is also a tendency toward the disappearance of the terminal branches. The arteries are extrinsically deformed by the cysts.

Cyst or Tumor[98]. The differential diagnosis between renal cyst or tumor has always been the bane of the urologist and radiologist. It has been their custom not to attempt differentiation but to mention both possibilities on an equal basis. The coupling of the two entities is considered an indication to operate. If the vascularity of the kidney can be well demonstrated as commonly accomplished by aortography, the two lesions often can be differentiated. The cyst appears as an avascular structure without traversal by vessels of significant size; malignant tumors, notably hypernephroma, frequently have a characteristic stippling or "tumor stain"[36] due to the puddling of opaque media in many newly formed small blood vessels. Billing[11] found these blood vessels to be pathological arteries without elastin in the walls. They vary in diameter from 1 to 4 mm. and in length from 4 to 10 mm. Papillary adenocarcinoma and squamous cell carcinoma of the renal pelvis usually do not exhibit these abnormal vessels. Wagner[123] has seen a tumor stain in a case of liposarcoma.

Embolus and Thrombosis of the Renal Artery. Clinically obstruction of the renal artery due to embolus or thrombosis[105] is a difficult diagnosis to make. Melick[87] claimed to be the first to show an embolus of the renal artery by aortography. Both embolus and thrombosis frequently lead to kidney infarction. Total infarction of the kidney is very unlikely. The following triad of findings may indicate kidney infarction:

1. Damaged kidney function shown by excretory urography
2. Intact kidney pelvis on retrograde pyelography
3. Diminution in the size of the kidney.

Goldblatt Kidney. The detection of an impaired blood supply to the kidney or a portion of the kidney is of great importance in a few but highly significant cases of hypertension[33,66]. Some of these individuals can be cured by the removal of the diseased kidney. The history of these patients frequently reveals a relatively acute onset of hypertension and it is often preceded by an episode of abdominal pain or trauma. In one recorded case the diagnosis was suspected by the diminution of kidney size over a period of 2 months[66]. Several cases have been diagnosed only by aortography. Of these, one showed a stenosing effect of the right renal artery. Another patient, a child, showed a ganglioneuroma compressing the left renal artery[66]. It has also been noted that the main renal artery may be normal but an aberrant vessel to one of the poles of the kidney is occluded and produces an infarction[20]. Of clinical importance in the diagnosis of the Goldblatt kidney is the differential measurement by ureteral catheter of urine volume and sodium

concentration. The involved side usually excretes considerably less urine with less sodium concentration than the uninvolved side.

Renal infarction may be single or multiple and usually is demonstrated on aortography by an abrupt termination of arterial branches with an avascular segment of parenchyma beyond. It is felt by some workers that the necrotic tissue of the infarct is relatively innocuous but the zone of diminished viability surrounding the necrotic cells is responsible for the liberation of some substance which acts as a hypertensinogen.

Nephrogram. A nephrogram is a film which shows opacification of the renal parenchyma by contrast material. It is a frequent by-product of abdominal aortography and is present within several seconds after the major blood vessels are filled with contrast substance[9]. The phenomenon of nephrography is quite familiar to urologists and to radiologists. It occurs occasionally in ordinary excretory urography especially when there is urinary stasis whatever the cause. It also occurs with regularity when highly concentrated intravenous opaque media such as 70% Urokon or Diodrast is employed. The nephrogram does not occur when the kidney function is seriously and irreversibly damaged.

While some physicians believe that the opacification of the kidney parenchyma is due to the presence of contrast medium in the smaller vessels, it is much more likely to be a function of the relatively high concentration of opaque medium in the tubules of the kidney. The opacification usually disappears after the bladder is well filled with contrast substance. The phenomenon implies a considerable degree of integrity of circulation and function of the renal tubular system.

The nephrogram, thus far, has been used rather grossly in diagnosis to compare one kidney with the other. Both Hellmer[62] and Doss[38] point out the possibility of utilizing the nephrogram in a more refined manner. They indicate that in one kidney, the normal portions may opacify, but a focal lesion such as an infarct, tumor, or cyst will not become homogeneously opaque. Instead it will appear as a relatively radiolucent area well demarcated from the opaque normal portion. An infarcted portion of the kidney may be suspected if the lesion is wedge shaped and contraction has occurred. On the nephrogram alone, cysts and tumors cannot be differentiated since they are both expansile lesions and would appear identically radiolucent. However, the earlier aortographic film which demonstrates the parenchymal vessels frequently allows a differential diagnosis.

DISEASES OF THE ABDOMINAL ORGANS. Enlargements and tumors of many abdominal organs have been detected by aortography. The spleen and occasionally the liver may be rendered opaque to Roentgen ray because of the large concentration of contrast medium within the parenchymal blood vessels. Splenic enlargements, accessory spleens, possibly rupture of the spleen may be revealed by injecting contrast substance close to or into the celiac axis. Several primary and metastatic tumors of the liver were diagnosed by noting the displacement of the hepatic artery. Nelson[92] intimates on the basis of one observation that the cirrhotic liver is associated with enlarged mesenteric vessels.

Tumors of the adrenal, either pheochromocytoma or cortical carcinoma can be appreciated by the extrinsic displacement of adjacent blood vessels or by the observation of the size and distribution of the suprarenal arteries. Other diseases in the abdomen, usually tumors, have also been recognized on

the aortogram[27,35,45,59]. Among these are para-aortic Hodgkin's nodes, metastatic seminoma, retroperitoneal masses, metastatic melanosarcoma, bladder tumors, ovarian cysts, and abnormalities of the corpora cavernosa. One case of uterine myomata was seen[54]. The maternal circulation of the placenta was studied by two observers[24,60,61]. Of course, it should be emphasized that simpler and more conventional methods, such as a plain film of the abdomen, gastrointestinal series, and barium enema, should be considered before abdominal aortography is utilized.

THE TECHNIQUE OF TRANSLUMBAR ABDOMINAL AORTOGRAPHY[43,44,121]. *Preparation of Patient.* Breakfast or the meal preceding the examination is withheld. For premedication appropriate doses of Demerol or morphine sulphate and scopolamine or atropine are injected approximately ¾ hour before the procedure. A 14 x 17 inch scout film is taken to insure proper technique and position. Average exposure factors for a patient measuring 24 cm. are 300 milliamperes, 1/10th of a second, 94 KVP, and a 36 inch target-film distance.

Anesthesia. With increasing experience, more examinations are done with the pre-medication and local anesthesia, using ½% procaine or xylocaine. After the skin and subcutaneous tissues are anesthetized, an attempt is made to infiltrate the para-aortic tissues. With proper technique, very little pain is experienced by the patient. Many investigators use intravenous sodium pentothal anesthesia supplemented by gas oxygen.

The type of needle recommended is a 17-gauge 6-inch needle with stylet #462 LNR. A short adaptor is fashioned from a 6-inch polyethylene tube with a 2 mm. inside diameter. The advantage of a polyethylene tube is its transparency. On one end of the polyethylene tube is placed a B.D. one-way female stop-cock #L-S4 and on the other end is placed a male luerlock slip hose end for 1/16 inch special #608 L. A 20 or 30 cc. luerlock syringe is employed to inject the opaque medium.

Examination. With the patient in the prone position, the site of injection is surgically prepared and the patient draped. To visualize the celiac axis, renal arteries, and upper abdominal vessels, the needle is inserted rather high in the aorta, usually at the level of the 12th thoracic vertebra. To reach this portion of the aorta, the needle is thrust through the skin 8 cm. to the left of the midline just below the 12th rib. The needle is then directed approximately 45° ventrally and about 30° cephalad parallel to the lower border of the 12th rib. If contact is made with the vertebral body, the needle is retracted slightly and the angle is changed so that the bony structures are barely grazed. When the aorta is entered, a slight decrease in resistance is encountered, and a pulsating blood flow is noted as the obturator is removed from the needle. The syringe, polyethylene tubing and the needle are flushed from time to time with physiologic saline solution.

The examiner is cautioned against inserting the needle into the orifice of the superior mesenteric or the renal arteries or even too close to the renal arteries. Damage to the kidneys has resulted from forceful and direct injection of various contrast substances. To be certain that the tip of the needle is in the aortic lumen and not too close to the renal arteries or other branches, a test dose of 5 cc. of 70% Urokon is injected and a film is exposed as the last cubic centimeter is injected. This film is observed wet. During the waiting period, the patient can be watched for symptoms and signs of hypersensitivity.

For the regular examination 10 to 30 cc. of Urokon is used depending upon the size of the patient and the points of maximum interest. The speed of the injection may vary from 1½ to 3 seconds. Usually as the last few cubic centimeters are injected the exposure is made. After approximately 7 seconds another film is exposed to show the nephrogram and evidence of delay in the circulation. An excellent excretory urogram can be obtained after 5 minutes. It is recommended that the injection be carried out by hand rather than by a mechanical injector. Many authors have used mechanical injectors which achieve great velocity and also trigger the exposure[19,34]. It is felt that renal complications are more likely with the use of mechanical injectors[89].

The level of the injection should be varied according to the main point of interest. For the upper abdominal vessels one should direct the needle to the 12th thoracic vertebra parallel to and just below the 12th rib. The level of the 1st lumbar vertebra is too close to the renal arteries. If the examiner is interested in the lower branches of the aorta, such as the inferior mesenteric arteries, or if he wishes to study the arteries of the pelvis and lower extremities[81], including the lower legs and feet, he should attempt to inject the opaque medium into the aorta at the level of the 2nd or 3rd lumbar vertebra. One should still insert the needle 8 cm. lateral to the midline just below the 12th rib and then direct the needle in a direction perpendicular to the lumbar spine. At this level the upper abdominal vessels do not drain off opaque medium.

It is noteworthy that the lower abdominal aorta is not fixed and may be tortuous. These factors may cause difficulty in gaining entry. If this situation arises the needle can be redirected to the 12th thoracic vertebral level where the aorta is fixed by the diaphragm and is more constant in position.

Johnstone[67] presented an analysis of his experience with serial abdominal aortography. He found that the aorta remains outlined for 3 or 4 seconds corresponding to the time of injection. One film usually stands out from the rest. Visualization of the peripheral branches is variable and may precede or follow optimum filling of the aorta. The distribution of the opaque material depends on the level of injection, direction of flow, and anatomical variations of the vessels. The aorta, splenic and renal arteries are best seen at 2.5 seconds after injection, the renal and splenic outlines at 7.5 seconds after injection, and the portal vein at 10 seconds after injection. In 2 cases a splenic venogram was obtained and in one case the portal vein, portal radicals and liver were shown. In other cases, the renal and inferior mesenteric veins were faintly outlined.

Variations in Technique. Stereoscopic films taken on one or two injections may aid in localizing the blood vessels more accurately[97]. A long cassette 14 in. by 34 in. in conjunction with a long stationary grid, has been employed to visualize the abdominal arteries simultaneously with those in the lower extremities. With the long cassette scanograms can be made by moving the Roentgen tube during the injection. The tube is fitted with a slotted lead diaphragm to produce a plane of Roentgen rays rather than a cone.

Dos Santos recommends the application of tourniquets to the legs in order to obtain better filling in the intraabdominal vessels. When the aorta is displaced to the right by a mass then the puncture should be approached from the patient's right side[80]. There are also advocates of the "two needle technique." This method employs two needles placed in the aorta side by

side. The advantages are claimed to be greater certainty that the needle is in the aortic lumen and also greater speed of injection.

Opaque Media[29]. Early in the development of aortography, many investigators used 100% sodium iodide solution as the opaque medium[39,58]. Since this solution was found to be quite painful and irritating[4], some workers employed Thorotrast[21,25,73,120]. Thorotrast, however, had the disadvantage of its radioactivity which produced late complications[7,69,72]. Organic iodine compounds such as Uroselectan, Abrodil, Perabrodil and Tenebryl were favored for a time[119]. Most modern investigators use 75% Neo-iopax, 70% Diodrast or 70% Urokon[14,128]. Urokon at the present time is in favor.

Aortography by Retrograde Catheterization of Femoral Artery. Fariñas[53,54], in 1941, developed a method of aortography in which a 1.5 mm. trocar was introduced into the femoral artery; a #5 or 6 F ureteral catheter was then passed into the aorta through the trocar. One advantage of this technique is that exact aortic levels can be chosen for injection[126]. This method has been further refined by Helmsworth[63] who uses a polyethylene catheter. Peirce[1,100-102] advocates the percutaneous insertion of a large needle into the femoral artery. A polyethylene catheter is then passed through the needle into the aorta.

COUNTER-CURRENT AORTOGRAPHY. Castellanos and Pereiras[17] claimed to have originated counter-current aortography in 1937. Counter-current flow is obtained by injecting opaque medium against the stream of arterial blood. The amount of counter-current flow is governed by the rate of injection, the arterial pressure, and the diameter of the vessel injected. The method is not very practical in abdominal aortography because of the large caliber of the aorta. Its main use lies in the visualization of the thoracic aorta in infants and children by the injection of opaque medium into an artery of the upper extremity.

Seaman[111] utilizing the angiocardiographic method obtained fair quality abdominal aortograms by triggering the exposure with small quantities of radioactive isotope. Of academic interest is Euhler's trans-esophageal technique[48]. He injects contrast material, with the aid of an esophagoscope, through the wall of the esophagus and into the aortic arch.

Complications[71,83]. There have been few serious complications in aortography and even fewer fatal reactions[85]. Dos Santos had 4 fatalities in his first 500 studies[23]. Since that time several series totaling over 7500 cases without a fatality have been recorded[70,86,116].

In recent years a few fatalities have been reported. Most of these have been due to renal damage or hemorrhage from the puncture site. The most serious complication of translumbar aortography is renal damage. Fourteen cases have been reported. In 6 cases the contrast substance was injected directly into one renal artery and that kidney was damaged[104]. In 8 cases the injection was made into the aorta and bilateral renal shutdown occurred. The majority of these cases had high aortic occlusion. Two of the 8 cases were fatal[23,55]. The injection was made directly into the renal artery in 11 other cases but no ill effects were observed[86]. Renal damage is probably due to direct irritation of the kidneys by the medium[89]. Pathologic changes observed have been interstitial fibrosis, generalized tubular atrophy, hyalinization of the glomeruli and renal infarction. The use of mechanical pressure injectors, the 2 needle technique of injection, or excessive quantities of contrast medium increase the risk of renal damage. All

3 of the commonly used media, Neoiopax, Diodrast, and Urokon, have been incriminated. Renal damage should be suspected if, following the aortogram, there is an abnormally dense nephrogram for a long period of time, excretion of the contrast medium in the biliary tract and a clinical picture of flank pain, anuria or oliguria, persistent vomiting and hiccoughs. Injection directly into the superior mesenteric artery should also be avoided. Wagner[124] reported a fatal case.

Hemorrhage. Dos Santos demonstrated that the aorta could be punctured with comparative safety. In several cases who died from other causes a few hours after the study, he was unable to identify the puncture site. Others have confirmed this finding[6]. They also observed that puncture of a calcified arteriosclerotic plaque was not particularly dangerous[50,131]. On the other hand, puncture of a thin-walled aneurysm may be a hazard. Bleeding from the puncture site with hematoma[122] formation is uncommon and usually not serious, but 2 fatal cases have been reported[83]. Contributing factors to hematoma formation are multiple punctures of the aorta, puncture of an aneurysm, and movement of the patient with the needle *in situ*.

Extra-aortic extravasation of the medium is not uncommon. It is not a serious complication with the newer contrast media. It is usually easily recognizable by the sudden onset of pain at the site of injection. The pain may last only a few minutes or up to 24 hours[28].

Anesthetic complications from general anesthesia may occur. This is of particular significance in aortography because there is a brief period of rather severe stimulation of the patient at the time of injection which requires a relatively deep anesthesia followed by a period of no stimulation. It is usual to observe a longer and deeper anesthetic depression after aortography than is seen in most surgical patients receiving a similar quantity of anesthesia[83]. On the other hand, local anesthesia carries with it a greater risk of the patient moving during the procedure. In general, a local anesthesia is preferable[57].

Complete motor and sensory paralysis of the spinal cord was reported in one case and was the result of ischemia secondary to compression of the aorta by a small pillow placed under the abdomen[3]. Air embolism has been mentioned as a possible complication[75], but no case has been reported. Perforation of an abdominal viscus has occurred a number of times but no complications have resulted[49]. It has been stated that the procedure is dangerous in children. However, the procedure has been performed on a number of children, the youngest being 5½ weeks old[84], and most workers feel that there are no particular hazards in performing aortography on children[56].

There are no absolute contraindications to aortography, with the exception of intolerance to contrast media and to drugs necessary for local or general anesthesia[115]. The presence of hypertension or impaired renal function may increase the risk of the procedure, but these cannot be considered absolute contraindications as they may be the very reasons for performing the study. Each patient should be carefully evaluated, however, and the appropriate simpler diagnostic tests should be done before aortography is undertaken[70].

Summary. Abdominal aortography, in common with angiocardiography and cerebral angiography, is a dynamic Roentgen method which demonstrates the lumen of a vascular system by the injection of radio-opaque contrast substances into the circulation. It is the method par excellence for the demon-

stration of vascular abnormalities of the aorta and its branches. Congenital anomalies, aberrant vessels, ectopic vessels, arteriovenous fistulae, aneurysms, thrombi, emboli, stenoses, occlusions, Leriche Syndrome, collateral circulation, atherosclerosis and thromboangiitis obliterans are demonstrated in a detailed and frequently definitive manner.

The kidney lends itself particularly well to analysis. Much information can be gained by aortography concerning such conditions as aplasia, hypoplasia, aberrant vessels, ectopia, duplication, horseshoe kidney, urinary stasis, hydronephrosis, ureteropelvic obstruction, calculus, tuberculosis, polycystic kidneys, cysts, neoplasms, infarct, and the "Goldblatt" kidney.

From the vascularity, inferences can be drawn concerning the status of certain abdominal and pelvic organs and structures. Diseases of the spleen, liver, adrenal, ovary, uterus, bladder, paraaortic and retroperitoneal tissues are recognizable.

There have been few serious complications in abdominal aortography and even fewer fatal reactions. In the few fatalities reported, most of these have been due either to renal damage or hemorrhage from the puncture site. The history and technique of abdominal aortography are also considered.

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BOOK REVIEWS AND NOTICES

CLINICAL PATHOLOGIC CONFERENCES OF COOK COUNTY HOSPITAL. VOLUME I. CARDIOVASCULAR-RENAL PROBLEMS. Edited by HANS POPPER, M.D., PH.D., Director, Dept. of Pathology, and DANIEL S. KUSHNER, M.D., Associate Director of Medical Education, Cook County Hospital. Pp. 325; 69 ills. New York: The Blakiston Company, Inc., 1954. Price, $5.00.

THE clinical pathological conference has justly earned its reputation as one of the most valuable of teaching exercises. A number of medical journals have recognized this and have incorporated transcripts of such conferences within their pages. To the reviewer's knowledge, however, this is the first time that a book of such conferences has appeared. The cases in this volume are selected from the wealth of pathological material available at the Cook County Hospital, and are entirely limited to those illustrating cardiovascular-renal problems. Subsequent volumes are to be published containing cases illustrating problems of gastroenterology, hematology, and metabolic and neoplastic disease.

Twenty-six conferences are included and each is well chosen for its teaching value. The 42 physicians who have participated in the discussion of the various cases have carefully edited the material, and their reasoning in working toward a diagnosis should prove valuable to any medical reader. The discussion of the pathological findings is amplified by comments dealing with interpretation in the light of the clinical aspects, and illustrated by excellent photographs of gross and microscopic material. Well selected references to the literature are appended.

Any physician who reads this book will find both pleasure and profit in its pages.

T. D.

ATLAS DER SYSTEMATISCHEN ANATOMIE DES MENSCHEN, VOL. I. BY GERHARD WOLF-HEIDEGGER, Prof. of Anatomy, University of Basel. Pp. 218; 345 ills. Basel: S. Karger, 1954. Price, 32 Swiss francs.

THIS book contains no written descriptions nor explanatory notes but is made up of 187 illustrations of the skeletal system on 94 pages, 50 illustrations of joints on 27 pages and 108 illustrations of the muscular system on 78 pages. The illustrations are clear with labelling which is satisfactorily complete and leaders which are readily followed to the correct structures. The extent of the coverage of the material compares favorably with that of other standard atlases of anatomy, although in some areas it is slightly less complete. The names used throughout are the Latin form of the Jena revision of the B.N.A.

J. H.

THE MICROTOMIST'S FORMULARY AND GUIDE. BY PETER GRAY, PH.D., University of Pittsburgh. Pp. 794; 87 ills. New York: Blakiston Company, 1954. Price, $10.50.

OVER the past 50 years the methods and techniques of preparing materials for microscopic examination have become greater and ever greater as each worker has added his special methods or modifications of already existing methods. The accumulated aggregate has become so massive that even specialists in the field find it difficult to keep their references straight.

"The Microtomist's Formulary" is the most complete reference book on this subject with which this reviewer is familiar. It contains hundreds of methods of fixation, preservation and mounting, both gross and microscopic, for almost anything which may find its way into the biologist's laboratory. There are several chapters dealing with the various types of preparation of tissues for microscopic examination and an attempt is made to diagnose the cause and give the remedy for some of the commoner of the technician's difficulties. Hundreds of stain formulas are listed and the technique for their use is briefly given. All of this material is catalogued with what to this reviewer seems to be a rather complicated decimal system. Perhaps further use and greater familiarity will minimize this complexity.

E. A.

THE UNCOMMON HEART DISEASES. BY NATHANIEL E. REICH, M.D., Clinical Assistant Professor of Medicine, State University of New York, College of Medicine. Pp. 516; 110 ills. Springfield, Ill.: Charles C Thomas, 1954. Price, $10.50.

A VERY large percentage of the cardiac patients seen by the physician may be quite readily classified as belonging in the more common etiologic categories, hypertensive, ar-

teriosclerotic, rheumatic, and others. There remains, however, an appreciable group in which the etiology is difficult to determine, and in some of these the possibility that the heart is involved by any one of a number of uncommon diseases is a good one. The physician frequently finds it necessary to search extensively through the literature in order to uncover the diagnostic information needed in such instances, particularly since many of the uncommon cardiac diseases are mainly represented by isolated case reports. Dr. Reich has very wisely recognized the need for bringing this important information together into a single volume, and he is to be congratulated on having carried out this arduous task extremely well.

There seem to be only a few respects in which this book is lacking. For maximum usefulness a volume which summarizes a wide range of unusual diseases needs a first-class index. One searches in vain for index reference to Fiedler's myocarditis, for example, though this term is used twice in the text. It is of interest, incidentally, that this form of myocarditis is considered to be a viral type of infection. One searches also for the terms Von Gierke's or Glycogen storage disease in the index though the condition is well covered in one of the chapters. In the text itself reference is made in a table to endarteritis obliterans as a cause of coronary occlusion, and the reader's interest is immediately whetted, but he finds no other mention of the subject anywhere. Many readers will wonder about the accuracy of the statement that 1.6% of all myocardial infarcts are due to syphilitic osteal stenosis. This may have been true some years ago, but certainly not today. There is no mention anywhere in the book of primary endocardial sclerosis, an obscure form of heart disease which has excited considerable interest in recent years.

These minor deficiencies do not, however, detract from the value of the volume as a whole, and the reviewer is certain that it will serve cardiologists, internists, and general practitioners as a reference book of great value. T. D.

MODERN PRACTICE IN ANAESTHESIA. Edited by FRANKIS T. EVANS, M.B., B.S., F.F.A.R.C.S., D.A., Consultant Anesthetist, St. Bartholomew's Hospital, London. 2nd ed. Pp. 622; 221 ills. New York: Paul B. Hoeber, Inc., 1954. Price, $12.50.

The author has performed an excellent service for the present-day physicians, not only for those who are anesthesiologists but for all physicians practicing medicine. He has collected and edited in one volume the combined knowledge and experience of twenty-six highly qualified anesthetists.

The author briefly but adequately presents all of the aspects of anesthesia. His manner of presentation is most interesting and the following sections are exceptionally well done: physiology of respiration, principles of muscular relaxation, the relaxants, balanced anesthesia and anesthetic emergencies.

This is one of the best texts in anesthesia that has been published. The entire subject of anesthesia is presented in a concise, complete and interesting fashion. L. K.

ATLAS OF EXFOLIATIVE CYTOLOGY. BY GEORGE N. PAPANICOLAOU, M.D., PH.D., Clin. Prof. of Anatomy, Emeritus, Cornell University Medical College. Pp. 245; 36 ills. Cambridge, Mass.: Harvard University Press, 1954. Price, $18.00.

THIS is a loose-leaf, leather covered monograph, the first portion of which is devoted to 57 pages of descriptive text. The atlas of colored plates is divided into sections embracing the female genital system, the urinary and male genital systems, the respiratory system, the digestive system, and shorter sections on exudates, the breasts, mitosis and miscellaneous. The colored drawings were done by Hashime Murayama. Each section is headed by a page or two of explanatory text and each plate is faced with a page of legends. The loose-leaf arrangement is designed to give space for supplementary material which is planned for the future.

It is conceded by all that Dr. Papanicolaou is the highest authority on the subject of exfoliative cytology. For those who have taken his course this atlas should be a valuable refresher and reference book. For the uninitiated and for those who are attempting to teach themselves the art of cytologic diagnosis this atlas presents the same pitfalls that does any atlas in pathology and hematology. The illustrations are so numerous and so similar that they lead to confusion rather than clear and definite concepts. Furthermore, an atlas of this type is apt to inspire unjustified confidence in the unenlightened which I am sure the author does not mean it to do. For this reason, this reviewer feels it should not be recommended to any except those who have attained a considerable experience in the field. E. A.

PNEUMOCONIOSIS ABSTRACTS, VOLUME II. Pp. 518. New York: Pitman Publishing Corporation, 1954. Price, $17.50.

THIS is the second volume of two that contain all abstracts of papers relating to pneumoconiosis that have been published in the Bulletin of Hygiene from the time of its first appearance in 1926 to the end of 1950. The present volume covers the period 1939-1950. They are arranged by topics in twelve chapters on the several types of pneumoconiosis, the sampling and measurement of dusts and of their significant properties, the protective measures against pneumoconiosis, legislation on the subject and book reviews. Research workers, teachers and industrial physicians, as well as students, will find this an invaluable reference work. R. K.

THE SURGERY OF PULMONARY TUBERCULOSIS. BY JAMES H. FORSEE, A.B., B.S., M.D. F.A.C.S., F.A.C.P., COL. MC., U.S. ARMY; Chief, Surgical Services, Fitzsimons Army Hospital, Denver, Colorado. Pp. 200; 59 ills. Philadelphia: Lea & Febiger, 1954. Price, $6.50.

THIS monograph on the surgery of pulmonary tuberculosis is written by a person who should be well versed in the treatment of pulmonary tuberculosis due to his extensive experience at the Army's tuberculosis center The monograph itself is concise and clearly points out the indications for surgery of pulmonary tuberculosis. Included also are the results of the experience at the Fitzsimons Army Hospital. The monograph properly emphasizes the marked increase in use of surgical means in the treatment of pulmonary tuberculosis and properly attributes this to the safety factor given by the use of antituberculous drugs. R. T.

THORAKOSKOPISCHE ENGRIFFE AM NERVENSYSTEM (THORACOSCOPIC OPERATIONS ON THE NERVOUS SYSTEM). BY DR. E. KUX PRIV.-DOZ., INNSBRUCK. Pp. 130; 51 ills. Stuttgart: Georg Thieme Verlag, 1954. (Grune & Stratton, New York, U. S. Agents). Price, DM 28.50.

THE author uses thoracoscopy in order to visualize and to operate upon the nerves passing through or lying in the wall of the thorax. This method permits one to approach the sympathetic chain, the splanchnic, the vagus and the phrenic in a much simpler way than by opening the thoracic cavity. The chief indications are peptic ulcer (in which condition the author applies combined vagosympathicotomy), angina pectoris, hypertension. He observed also a favorable effect of splanchnicotomy upon diabetes mellitus, probably due to increase of the sensitivity to insulin. Other suggested indications, such as pulmonary tuberculosis and icterus, are less clear. Some of the physiopathologic concepts of the author are outdated: for example, his belief that the anterior roots carry viscerosensory impulses. This does not, however, decrease the intrinsic value of this new method that deserves the attention of all surgeons interested in operative procedures on the autonomic system. E. S.

DIE UNSPEZIFISCHEN BLUTEIWEISSREAKTIONEN. BY DR. MED. FRITZ HEEPE. Pp. 241; 8 ills. Darmstadt: Verlag von Dr. Dietrich Steinkopff, 1953. Price, DM 30.

A well-written monograph on the nature, structure and reactions of the protein components of the blood, with detailed descriptions of numerous analytic and diagnostic techniques. Physiologists, chemists and hematologists, who read German, will find this a useful compilation. R. K.

TEXTBOOK OF THE NERVOUS SYSTEM. BY H. CHANDLER ELLIOTT, M.A., PH.D., ASSOC. Prof. of Anatomy, University of Nebraska College of Medicine. 2nd ed. Pp. 437; 158 ills., and an atlas of 50 plates. Philadelphia: J. B. Lippincott Co., 1954. Price, $9.00.

FOR the second edition, the author has made a complete revision; the principal changes being the expansion of the Atlas and the addition of many photographs and key drawings of transverse and sagittal sections of the brain stem. Other changes include a more detailed description of the neuron, and rewriting the sections on the reticular formation and the cerebrum.

Basically, the plan of the text is unchanged. The introductory chapters deal with the central nervous system in outline; the succeeding chapters consider its structure in greater detail. The "basic brain," a highly simplified diagram of the human brain, is used as a basis for many of the illustrations. Such simplified drawings are easily understood by one having some knowledge of brain structure but, in the opinion of the reviewer, the outline drawings are not adequately correlated with

the actual brain morphology in this text, written primarily for the beginning student.

Although the text presents much valuable information, and is unique in the amount of clinical neurology it contains, in many places it is subject to adverse criticism. The author's descriptions are given in a very interrupted manner, and there is a complete lack of correlation with the peripheral nervous system. Certain terms used are not conventional and in the chapter on Circulation, the anatomical information given is inadequate for students to understand clinical neurology.

However, the plan of the text is to be commended. Introducing the Nervous System in simplified outline form and the use of the "basic brain" diagrams, if supplemented with adequate material in the laboratory, should help the student obtain a fair concept of the central nervous system. Possibly these attributes outweigh the adverse criticisms offered above. D. K.

NOBEL PRIZE WINNERS IN MEDICINE AND PHYSIOLOGY, 1901-1950. BY LLOYD G. STEVENSON, M.D., PH.D. Pp. 291; 59 ills. New York: Henry Shuman, 1953. Price, $6.50.

THE author is to be complimented on this splendid collection of biographical sketches of the fifty-nine recipients of Nobel Prizes in the fields of Medicine and Physiology between 1901 and 1950, inclusive. Each article also contains a passage in which the prize winner describes the prize discovery in his own words and then a brief editorial explanation of the meaning and importance of the work. There are photographs of each prize winner. All physicians will find these sketches inspiring as well as interesting. R. K.

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75 YEARS OF MEDICAL PROGRESS. Edited by LOUIS H. BAUER, M.D. Pp. 286; 26 ills. Philadelphia: Lea & Febiger, 1954. Price, $4.00.

THE past 75 years have seen more progress in the field of medicine than the previous 3,000. In April, 1953, in Richmond, Virginia, there was held The First Western Hemisphere Conference of the World Medical Association and the theme of the Conference was the medical progress of the last 75 years. This volume, edited by Dr. Louis H. Bauer, Past President of The American Medical Association and Secretary-General of the World Medical Association, contains twenty chapters by 26 contributors, all of them leaders in their respective specialties, who outline the major advances in their several fields, beginning with Anesthesia and continuing alphabetically to Urology. Each section is extremely well done. The major problem that obviously confronted each author was, what to include of the vast material at hand in the limited space available? The reviewer amused himself in checking on the references to one topic that is quite new in the period mentioned: Allergy. There were extensive references in a number of special fields; notably Otorhinolaryngology, Ophthalmology, Dermatology, Proctology and Urology; but the subject was not once mentioned in the fields of General Practice, Internal Medicine and Pediatrics. This is not said in criticism, but merely to show the difficulties of selection that confronted the writers. The book furnishes fascinating reading. R. K.

CORONARY HEART DISEASE IN YOUNG ADULTS. A MULTIDISCIPLINARY STUDY. BY MENARD M. GERTLER, M.D., PAUL D. WHITE, M.D. AND OTHERS. Pp. 218; 26 ills. Published for the Commonwealth Fund. Cambridge, Mass.: Harvard University Press, 1954. Price, $5.00.

DURING the past two decades there has been an increasing recognition of the magnitude of the coronary disease problem in the young adult male. Realization of the fact that this group with unusual disease predisposition might provide important clues in the search for the etiology of atherosclerosis has lead many investigators to center their interest upon them. The interdisciplinary study reported in this volume began in 1946 under the auspices of 7 Boston physicians. Later expansion of the project led to the employment of Dr. Gertler as full-time director. One hundred patients under 40, suffering from "pure" coronary heart disease were thoroughly investigated from clinical, genetic, biochemical, anthropological and hormonal standpoints, the findings being correlated with information provided by a random control sample and a matched control group. These findings indicate that by taking into consideration sex, body build, morphological characteristics, heredity, serum total cholesterol, serum uric acid, plus several other indices and ratios, it should theoretically be possible to preselect coronary-prone individuals from the population. Such a development is indeed a great advance in the field of preventive medicine, and it is to be hoped that further observation will serve to confirm this. This

is a book which should be of great interest to all internists and cardiologists. T. D.

THE PHYSICIAN AND HIS PRACTICE. Edited by JOSEPH GARLAND, M.D., Editor, The New England Journal of Medicine. Pp. 270. Boston: Little, Brown & Company, 1954. Price, $5.00.

HERE is a book with much practical information that all physicians will enjoy and that recent graduates and senior medical students will find particularly helpful. The chapter headings tell their story: for example, Family and Community Relations, The Doctor's Wife, Choice of Opportunities, General Medicine, Specialty Practice, Group Practice, Doctor and Hospital, Medical Organization, Reading and Writing, Drugs and Medical Supplies, Office Records, Medicine and the Law, and others. The editor, Doctor Garland, is to be congratulated on the selection of his contributors and they on the excellence of their contributions. R. K.

MANUAL OF PROCTOLOGY. BY EMIL GRANET, M.D., Lecturer, Graduate School, Columbia University. Pp. 346; 119 ills. Chicago: The Year Book Publishers, Inc., 1954. Price, $7.50.

DR. GRANET, who is an active proctologist, has written a book which he hopes will give practical guidance in the examination, diagnosis and treatment of patients with proctological difficulties. His early chapters deal with the anatomy and physiology of the lower bowel and anal region. They include a very thorough discussion of the methods of examination in the proctologic diseases. The chapter on anesthesia includes a discussion of the long acting anesthesias and it is evident that he has not confined himself to proctologic therapy in the ambulatory patient. The remaining portion of the book is taken up with the discussion of the various proctologic lesions such as infections, fissures, fistulas, hemorrhoids, pilonidal cysts and rectal polyps. In his chapter on malignancy of the colon there are illustrations which would indicate that resection is not too radical in the treatment of such lesions. In the chapter on ulcerative colitis it is surprising to find that no description of the proctologic picture of this disease is given.

It is the reviewer's impression that the book has excellent sections in anal anatomy, physiology and in the treatment of anal lesions. When the author discusses lesions of the abdominal colon, he leaves much to be desired. L. F.

THE VITAMINS: CHEMISTRY, PHYSIOLOGY, PATHOLOGY, VOLUME I. Edited by W. H. SEBRELL, JR., National Institutes of Health and ROBERT S. HARRIS, Massachusetts Institute of Technology. Pp. 676; 76 ills. New York: Academic Press, Inc., 1954. Price, $16.50.

THE authors are to be congratulated on undertaking the task of gathering, collating and editing what is known about the vitamins. Numerous contributors discuss the phases of the subject in which they are particularly qualified. Special emphasis is given to the chemistry and physiology of the vitamins, while the clinical manifestations of the vitamin deficiencies and their treatment are not given in detail, since they are adequately covered in other publications. Methods of vitamin assay are also presented only briefly. The vitamins are arranged alphabetically and this, the first volume, has four chapters dealing with 1) Vitamin A and carotene; 2) Ascorbic acid; 3) Vitamin B_{12}; and 4) Biotin, which have been prepared by twenty-one writers. There are numerous references to source material; the illustrations are well done; and there is an excellent index. The book is warmly recommended. It is noted with pleasure that the remaining two volumes are due to appear before the end of this year. R. K.

NEW BOOKS

The Work of WHO, 1953. Official Records of the World Health Organization, No. 51. Pp. 190; 16 pages of ills. Geneva: World Health Organization, 1954. Price, $1.50.

A concise, interesting record of progress and achievement by an organization that continues to perform most valuable services to promote human welfare and therefore a better mutual understanding of nations: The World Health Organization under its able Director-General, M. G. Candau. R. K.

Problems of Consciousness. Transactions of the Fourth Conference, March 29, 30, and 31, 1953. Edited by HAROLD A. ABRAMSON, M.D. Pp. 177; 3 ills. New York: The Josiah Macy, Jr. Foundation, 1954. Price, $3.25.

THIS is the report of the Fourth Conference on Problems of Consciousness sponsored and publish-

ed by the Josiah Macy, Jr. Foundation. The aim of these conferences is to stimulate research and promote communication between different specialties concerned with the same problem.

There were 25 participants from the fields of clinical and experimental fields of psychology, medicine and other social sciences. The discussion centered around contributions by Roy Grinker, Talcott Parson and Jean Piaget. No conclusions were stated. O. E.

The Causes and Treatment of Backwardness. By Sir Cyril Burt, D.Sc., Emeritus Professor of Psychology, University of London. Pp. 128. New York: Philosophical Library, 1954. Price, $3.75.

This is a competent and readable book on the problems of the child who has difficulty in learning. The problems are discussed from many facets and could be read profitably by teacher, parent and physician. O. E.

William H. Welch and the Rise of Modern Medicine. By Donald Fleming. Pp. 204. Boston: Little, Brown & Co., 1954. Price, $3.00.

An account from the Johns Hopkins point of view of the important role played by Welch and his colleagues in the development and guidance of medical education and research in this country. As one of the series of the Library of American Biography, it appropriately views the individual and his times as forces reacting on each other, and at the same time finds room to introduce refreshing personal touches, pro and con, that throw interesting light on these much written-up characters. E. K.

Schemata der Leitungsbahnen des Menschen. By Eduard M. W. Weber, Medizinische Poliklinik der Universität München. 6 tables. Munich: J. F. Lehmanns Verlag, 1954. Price, DM 7.00.

In 6 tables the distribution of the arteries, veins, spinal, cranial and autonomic nerves as well as the tracts of the central nervous system are represented. Unfortunately, the diagrams are so schematic that they represent little more than enumeration of the various structures. Their didactic value, if any, seems therefore to be rather limited. E. S.

The Painful Phantom. By Lawrence C. Kolb, M.D. Pp. 50. Springfield, Ill.: Charles C Thomas, 1954. Price, $1.50.

This is a concise monograph, written by a psychiatrist, on the physiologic, neurologic and psychiatric phenomena concerned with the phantom limb syndrome. He calls attention in a clear way to the many different attitudes and fantasies surrounding amputation which are best dealt with prior to surgery if possible. Emotionally healthy people "accept their defect, resume their family position, return to their occupation and, with an adequate stump, make use of an appropriate prosthesis. Failure . . . to make these adaptations suggests . . . a personality disturbance." The author advises selecting these and coping with them psychiatrically in the early post-operative period. O. E.

Proceedings of the Society for the Study of Fertility, Number V. Liverpool Conference, 1953. Pp. 105; illustrated. Cambridge, England: W. Heffer & Sons Ltd., 1953. Price, 10s.

This report of the Proceedings of the Society for the Study of Fertility consists of the papers read at the Liverpool Conference in 1953. There is no discussion. Both clinical reports and experimental work are included and the subject material is highly diversified although all related to the basic problem of fertility. Some of the papers present the results of technical physiologic or anatomic studies in animals but more than half deal with clinical aspects such as the study of tubal patency and the investigation and treatment of the infertile male. The papers will undoubtedly be of greater interest to the specialist in the study of sterility than to practicing physicians. J. W.

The Synthesis and Physical-Chemical Properties of New Aromatic Amidines. By Martin Kuna and M. J. Kopac. Ann. New York Acad. Sci., Vol. 58, Art. 3. Pp. 31. New York: New York Academy of Sciences, 1954. Price, $1.00.

NEW EDITIONS

Anatomy of the Human Body. By Henry Gray, F.R.S., Late Fellow of the Royal College of Surgeons. Edited by Charles Mayo Goss, M.D., Professor of Anatomy, Louisiana State University College of Medicine. 26th ed. Pp. 1480; 1202 ills., mostly in color. Philadelphia: Lea & Febiger, 1954. Price, $16.00.

A work that has reached its 26th edition, 96 years after the appearance of the first needs no introduction to the profession. The editor is to be congratulated on the timeliness and excellence of the revisions as well as the preservation of elements that were responsible for the past success of the work. The publishers have produced a fine volume, worthy to stand besides its predecessors. R. K.

Laboratory Experiments in Physiology. By W. D. Zoethout, Ph.D., Prof. Emeritus of Physiology, Chicago College of Dental Surgery, Loyola University. 5th ed. Pp. 260; 96 ills. St. Louis: C. V. Mosby Co., 1954. Price, $3.50.